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The Nutrition of the Cancer Patient

Sponsored by the National Cancer Institute's Diet, Nutrition, and Cancer Program and the Division of Cancer Treatment

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January 10-11, 1980

Editors: Daniel L. Kisner, M.D. and William D. DeWys, M.D.

The Nutrition of the Cancer Patient

Daniel L. Kisner*[1]

Malnutrition and wasting are frequently associated with malignancy and often are the cancer patient's most debilitating problems. Nixon, et al (1) recently reported a survey of the nutritional status of 54 hospitalized cancer patients utilizing anthropometrics, creatinine-height indices, and serum albumin. Virtually all of this admittedly select population exhibited loss of adipose tissue, visceral protein, or skeletal muscle. The frequency of weight loss in a large series of cancer patients entering chemotherapy protocols ranges from 40% for patients with breast cancer, acute myelocytic leukemia, and sarcoma to more than 80% in patients with carcinoma of the pancreas and stomach (2). About 60% of patients with carcinomas of the lung, colon, or prostate have experienced weight loss prior to beginning chemotherapy (2). In a recent analysis of the impact of the existence of any pretreatment weight loss in 12 chemotherapy protocols of the Eastern Cooperative Oncology Group, it has been shown that weight loss was associated with significantly shortened survival in patients with non-Hodgkins lymphoma, sarcomas, and carcinomas of the breast, colon, prostate, lung, and stomach (2). This correlation with weight loss was found to be independent of disease extent and performance status, thus establishing pretreatment malnutrition (weight loss) as an independent prognostic factor in chemotherapy studies.

This malignant cachexia is partially related to reduced caloric intake. Although mechanical problems in the gastronintestinal tract may occur, the principal cause of reduced caloric intake is tumor-related or treatment-related anorexia.

Animal studies have repeatedly documented reduced food intake with weight loss in cancer-bearing rodents (3). This has been confirmed in some human studies (4). However, one recent report, in lung cancer, demonstrated no difference in food intake between patients losing weight and those with stable weight (5). This report notwithstanding, it seems reasonable to assume some role for reduced caloric intake in most patients losing weight. The mechanism of this tumor-related anorexia has not been clearly elucidated. Recent animal studies pertinent to the topic have implicated an abnormally increased synthesis of hypothalamic serotonin with resultant stimulation of the satiety center (6). This was apparently due to increased free plasma tryptophan levels. Intracisternal administration of serotonin antagonists has increased food intake in these tumor-bearing animals. Limited human studies also suggest increased plasma free tryptophan levels in cancer patients as well, raising the possibility of the therapeutic use of serotonin antagonists (6).

Recent work has also shed light on the problem of treatment-related anorexia. Both animal and human studies have demonstrated that conditioned (learned) food aversions can develop to foods fed temporally close to chemotherapy administration (7,8). The overall importance of this phenomenon is not yet established and work continues.

Similarly, acquired food aversions have been demonstrated in animals receiving whole or partial body radiation. This phenomenon has been shown to be related to histamine release and is prevented by antihistamines (9,10). Work is continuing to determine if this phenomenon occurs in cancer patients receiving radiation.

Superimposed upon reduced food intake are a host of metabolic disturbances found in cancer patients that probably increase basal energy requirements and produce inefficient utilization of ingested nutrients. Glucose intolerance systemic and specific tissue insulin insensitivity have been documented (11,12), along with increased gluconeogenesis (13), increased Cori cycle activity (14), and reduced glycogen synthesis (12). These phenomena would tend to decrease the patient's efficiency in utilizing carbohydrates as an energy source, and reduce his ability to adjust normally to periods of intermittent fasting. Recent work has also demonstrated reduced peripheral muscle protein synthesis and increased activities of protein catabolic enzymes (15). Increased protein turnover and poorly regulated amino acid oxidation may also be important (16).

The overall roles of reduced caloric intake and metabolic disturbances in the development of malignant cachexia must be regarded as unsettled, and future research in this area is critical to the development of specific therapeutic interventions for cachexia.

The treatment of malignant cachexia remains a frustrating problem. Both animal (17) and human (18) studies suggest that nutritional support is largely

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ineffective in repleting lean body mass in the cancer-bearing host. Randomized trials exploring the usefulness of total parenteral nutritional support (TPN) as an adjunct to cytotoxic antineoplastic therapy have not, to date, demonstrated any improvement in treatment results. This, along with the clear demonstration that TPN can stimulate tumor growth in animals (17,19), suggests that the routine use of TPN in cancer treatment is not justified. Continued research is required to explore the possible role of TPN, including its potential to enhance the effect of cycle active cytotoxic therapies by altering tumor kinetics in humans.

These recent advances, among others, and the new issues they raised, prompted the National Cancer Institute's Diet, Nutrition, and Cancer Program and the Division of Cancer Treatment to organize this symposium on the nutrition of the cancer patient. The intention is to outline the current understanding of anorexia and host/tumor metabolism, and to review the most recent work dealing with the use of nutritional support in cancer patients. While relatively few final statements can be made, it will be apparent that considerable progress has taken place that will open the way to more definitive research.

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Anorexia and Weight Loss in Cancer Patients[1]

Giovanni Costa,* Patricia Bewley, Miriam Aragon, and Julie Siebold[2]

SUMMARY

Food intake was estimated on 205 normal subjects and in 199 cancer patients. Decreased food intake was demonstrated in male, but not in female, cancer patients. In a subset of male lung cancer patients with well-documented weight history, anorexia could not explain weight loss.

[Cancer Treat Rep 65 (Suppl 5):3–7, 1981]

Clinical experience suggests that weight loss and cachexia occur frequently in cancer patients. More recently, weight loss has been recognized as one of the major determinants of survival (1–5), a fact that makes the understanding of its pathogenesis of prime clinical relevance. Many factors are involved, however (6), and few scientific studies document the interrelationships.

Anorexia is certainly one of the more likely pathways and there is no question that in some patients spontaneous consumption of food decreases to such an extent that host depletion ensues. These patients are often afflicted by advanced cancers and present with mechanical obstruction of the gastrointestinal tract. Whether anorexia plays a role in patients with less advanced disease is unproven, since precise data on the incidence, degree, and timing of anorexia in cancer patients are still lacking. Moreover, no firm data have been reported concerning the relation of anorexia to weight loss.

In the present paper, we have studied food consumption in 199 ambulatory cancer patients and in 205 matched controls. Our data show that male cancer patients eat significantly less than their controls. In a smaller but more homogenous subset of male lung cancer patients, anorexia and weight loss were found to be unrelated.

MATERIALS AND METHODS

One hundred ninety-five ambulatory patients with a variety of cancers were studied. Patients were enrolled in Dr. R. Cooper's clinic in the Thoracic Clinic at Roswell Park Memorial Institute. Patients studied were free from brain metastases or intestinal obstruction. None had received irradiation to the head and neck and none were being irradiated. Most of the patients were included in various chemotherapy programs. All patients who met the above criteria and were willing to participate were included in the study.

Seventy-six normal males and 129 female employees of a local industry, aged 20–65 years, generously volunteered for a nutrition interview that included a medical and weight history, measurements of height, anthropometric parameters, and estimates of food intake by the 24-hour recall.[3] The subjects were also instructed on the compilation of a 3-day diary to include either a Saturday or a Sunday.

Dietary intakes were estimated by two different techniques applied to both groups, 24-hour recall and 3-day diary. Standardization of the techniques and certification of the dietitians were achieved through the facilities of the Diet, Nutrition and Cancer Program (DNCP) of the National Cancer Institute. Coding of food consumed followed the DNCP guidelines (7). Amounts of food consumed were converted to amounts of nutrients using Department of Agriculture Manual No 8 (8) and Church and Church (9). In 35 patients, amounts of nutrients were also obtained using the DNCP computer code (7). In these 35 patients both conversion techniques produced essentially equivalent results.

[1]This study was supported in part by the Margaret Duffy and Robert Cameron Troup Fund of the Buffalo General Hospital, grant RD-79 from the American Cancer Society, and contract No. N01-CP-65834 from the Diet, Nutrition and Cancer Program, National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

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[3]The authors are grateful to the management and the nurses of Fisher-Price Toys, East Aurora, New York, for allowing and encouraging our study of their employees.

Although all subjects returned their 24-hour recall, only about 60% produced their 3-day diaries. Comparison of the two techniques in these patients yielded practically identical average amounts of food consumed (10). In the present paper the data are therefore displayed as 24-hour recalls, unless otherwise indicated.

RESULTS

Average food consumption by normal males, normal females, male cancer patients, and female cancer patients is shown in figure 1. The data clearly show that male cancer patients ate significantly less than the healthy controls (1894 kcal/day vs 2358 kcal/day, $P < 0.005$). Female cancer patients maintained their food consumption near the level of their normal counterparts (1556 kcal/day vs 1612 kcal/day).

The relation between food intake and weight loss was analyzed in male lung cancer patients, who represented the single largest subgroup of patients. Lung cancer patients were classified as "losers" if they had lost or "keepers" if they had not lost, within 60 days, at least 5% of the weight at first encounter (which was, for all practical purposes, synonymous with weight at diagnosis) (5). Food consumption of controls, keepers, and losers is shown in figure 2. Although both subgroups of cancer patients ate less than the controls, the patients who lost weight did not eat less than the patients who maintained their weight.

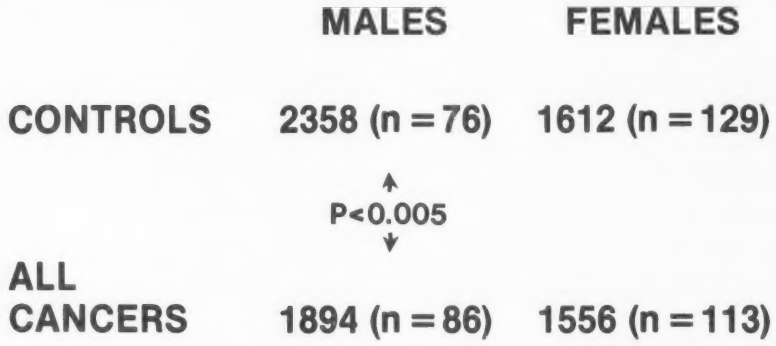

FIGURE 1.—Average food intake (cal/24 hr) of cancer patients and normal controls.

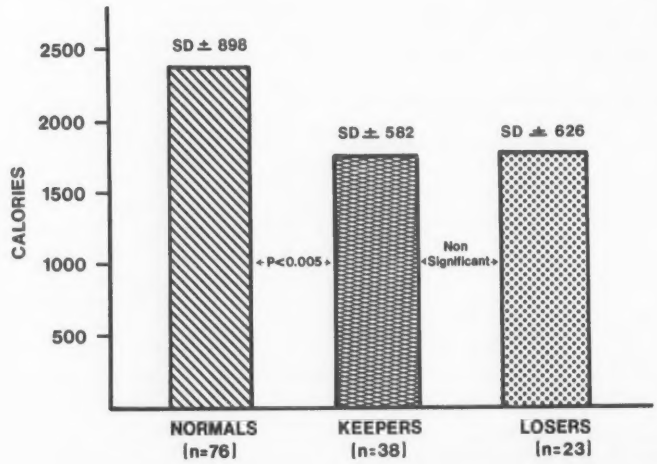

FIGURE 2.—Food intake of normal male controls and of male lung cancer patients by weight loss categories. (*See* text for definition of keepers and losers.)

Figure 3 shows average weight of controls, keepers, and losers, in addition to the ratio between caloric "intake and basal energy expenditures (BEE) calculated according to the nomograms" of Boothby and sandiford (11). A significant loss of weight (keepers, average 173 lbs; losers, average 150 lbs; $P < 0.01$) was not associated with differences in food intake or in the Intake/BEE ratios.

DISCUSSION

The relationship between weight loss and food intake among cancer patients is important, since it affects our intervention strategies (12). It is indeed reasonable to expect that weight loss due to insufficient intake or to abnormal loss of nutrients might be reversed by currently available techniques of hyperalimentation and it is plausible to infer that with these techniques, survival might be improved. It is not reasonable, however, to expect that hyperalimentation will be useful if the weight loss is due to distant, paraneoplastic effects of cancers interfering with the metabolism of the host.

To resolve this question, we have studied the spontaneous food consumption of male and female volunteers. Our estimated intakes (males, 2358 kcal/day; females, 1612 kcal/day) are nearly identical to those of larger surveys, such as the Hanes Study (males, 2301 kcal/day; females, 1533 kcal/day) (13).

Our data also show that food consumption of male cancer patients is sharply reduced. Again, our data are similar to those obtained by Valdivieso (14) and those reported by DeWys et al for a multi-institutional study (15). Female cancer patients, much to our surprise, maintained their food consumption.

The relationship of food consumption to weight loss was studied in the subset of patients represented by male patients with lung cancer, the most numerous subset. Lung patients also allowed survival consideration. As described elsewhere (5) lung cancer patients lose weight in one of two ways. There are patients who lose weight early in their disease and rapidly ($\geq$ 5% of weight at or about diagnosis within the first 60 days) and there are patients who lose weight only much later, when their disease is widespread. We have labeled these two types of patients "losers" and "keepers" (5). The survival of keepers and losers is shown in figure 4.

Because their weight history was known, patients with lung cancer could be allocated to the appropriate weight loss category.

Our data show that, in this particular subgroup of patients, reduced food intake could not account for a substantial reduction in weight, from an average 112% of ideal weight (average weight, 173 lb) to 96% of ideal weight (average weight, 150 lb). It is unlikely that a true difference in intake would have been missed. Figure 5 shows daily consumption by 49 young (average age, 33 years) normal females and 40 older (average age, 52 years) women with cancer. The figure shows that either technique yields the same result within each group and could detect a difference of about 300 kcal/day between groups. The conclusion that changes in food intake alone are inadequate to explain weight loss in the patients described is compatible with recent reports indicating inability of hyperalimentation to increase the lean body mass of cancer patients (14,16,17). Whether these considerations are applicable to other tumor types, or even to lung cancer patients later in their disease, remains to be proven. The inability of anorexia to explain weight loss in these patients raises the possibility that weight loss is a consequence of altered host metabolism.

Animal models and recurring clinical reports indicate that energy requirements of the host are increased, either because of acceleration of wasteful cycles or

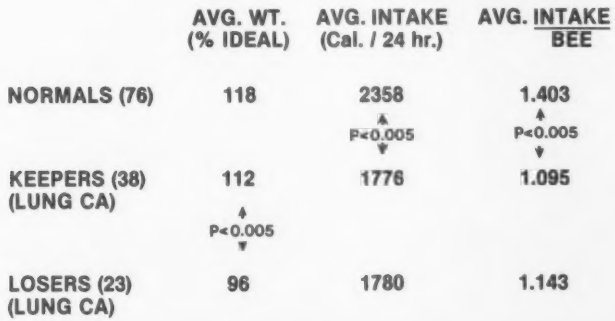

FIGURE 3.—Relationship between caloric intake and weight changes and the ratio between intake and BEE for normal males and male lung cancer patients. (*See* text for definition of keepers and losers.)

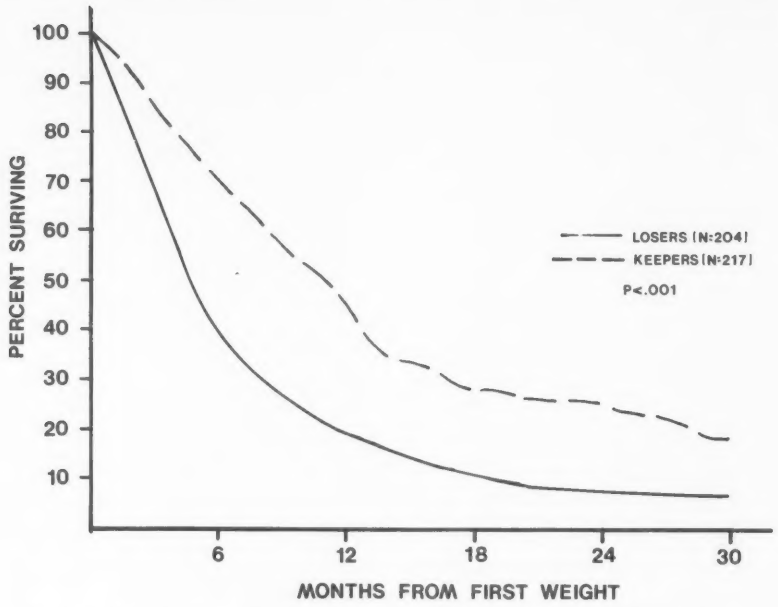

FIGURE 4.—Survival of lung cancer patients by weight loss category. (*See* text for definition of keepers and losers.) Reproduced from Costa et al (ref 5).

CALORIES

	Normal Volunteers	Cancer Patients	
24 hr. Recall	1755 ±594	1457 ±600	t=2.3 p=0.02
3 Day Average	1750 ±484	1469 ±402	t=3.1 p=0.01
	t = 0.2 p = NS	0.1 NS	

FIGURE 5.—Average daily intake (in cal/24 hr) of 49 young normal volunteers (average age, 33 yrs) and 49 older female cancer patients (average age, 52 yrs) studied by two different techniques.

because of abnormalities in the normal metabolic regulators (18-26). Reports that inefficient fuel utilization explains weight loss are suggestive, but the techniques used are somewhat questionable and often based on unproven assumptions.

Because it is becoming clearer that weight loss in cancer patients might not be due in all cases to inadequate food intake, definitive studies aimed at defining the metabolic abnormalities of cachexia are needed, are within the domain of existing technology, and should prove to be a valuable field of investigation.

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Control of Food Intake in Experimental Tumor Growth

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SUMMARY

The cachectic depletion of cancer is invariably an immediate consequence of progressive deficit of food intake below metabolic cost. The deficit of food intake arises from successive impairment of individual feeding controls. The impairment of some feeding controls well before there is overt hypophagia or cachexia indicates that overt cachexia is preceded by a silent or compensated cachectic process, and behavioral compensation for deteriorating feeding controls can be demonstrated. The hypothalamic components of control of food intake are not affected. In some instances, severe asthenic reduction in motor activity further disables capacity to feed since feeding is a motor activity and motor capability is a necessary condition for feeding. The variability in timing and severity of cachectic decay among different tumors and individuals is a function of the timing and sequencing of breakdown of individual controls, capacity for compensation, and impairment of motor capability, and the extent to which all possible controls are functionally expressed in the normal individual.

[Cancer Treat Rep 65 (Suppl 5):9–14, 1981]

The development of cancer cachexia is very variable among tumor types, both clinically and experimentally. Clinically, the spectrum ranges from those cancers that are regarded as noncachectic (eg, breast cancer) to those in which the cachectic depletion is almost invariable (eg, lung cancer). Most experimental tumors that kill the host produce some degree of cachexia, but this varies from a slow and prolonged to a sudden and precipitate depletion (fig 1). Even within a single tumor type the time of development, the detailed course, and final extent of the cachexia vary greatly. This variability is one of the many difficulties in the study of the origin of cachexia.

The central and definitive feature of cachexia is tissue depletion involving, for the tumor-bearing host, a negative nitrogen balance and, for both the host and the whole tumor-bearing organism, a negative energy balance (fig 1) (1,2). There is some clinical evidence that the metabolic rate of the host may sometimes be elevated (3,4) and that energy intake of cancer patients who are losing weight may sometimes be higher than the intake of those who are not losing weight (5). In experimental animal tumor systems, there is no convincing evidence of raised metabolic rate of the host and usually there is an absolute decline of food intake (1,2). However, neither an absolute change in energy cost nor in food intake is necessary for cachectic depletion. The essential deficit in producing cachectic or any other kind of tissue depletion is that intake falls short of cost. It is the magnitude and sign of the balance that is important in this respect, not the detailed behavior of the terms of the balance. If the energy cost were to increase, there would be no depletion if the food intake behaved as it does in physiological states, that is, rose to meet the increased cost. If absolute food intake increases while there is ongoing tissue depletion, then the increased food intake must represent a relative hypophagia (anorexia), in the sense that intake is falling short of metabolic need. Hypophagia, absolute or relative, is a necessary and invariable feature of cachexia. Failure to eat (or to eat enough) is obviously not the total cause of cachexia, otherwise the syndrome would be identical with that of uncomplicated starvation (6), but it is the primary and immediate cause of the cachectic depletion.

IMPAIRMENT OF FEEDING CONTROL

Since the food intake fails to meet the costs, there must be an alteration in the control of food intake. This does not necessarily imply impairment of control. It is

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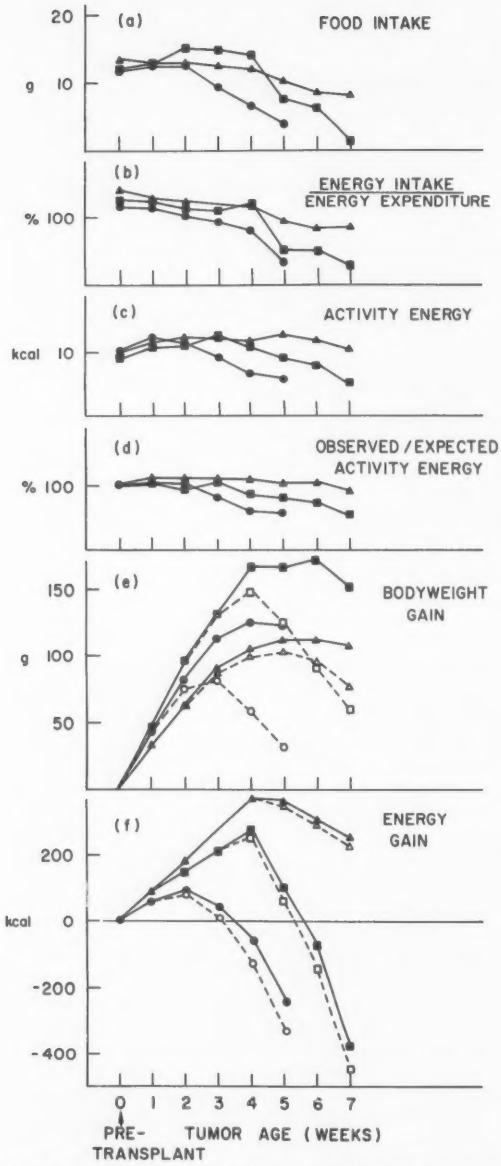

FIGURE 1.—Development of cachexia, including change in food intake and in some components of energy exchange during growth of three different experimental, transplantable tumors in adult male rats. ●○ Walker 256 carcinoma growing in Sprague-Dawley rats (S-D/W256 organism); ■□ 4M carcinoma growing in Sprague-Dawley rats (S-D/4M organism); ▲△ Morris 5123 hepatoma growing in Buffalo rats (B/H5123 organism). Solid symbols and lines are total organism (host plus tumor); open symbols and broken lines are host only, (fig from ref 22)

conceivable that the depressed intake relative to cost is functionally appropriate. Whether a change in food intake is appropriate or inappropriate is an aspect of the control of feeding that has not, so far, been given much analytical attention. As a very coarse first condition we could say that a food intake that leads to imbalance would be appropriate if it enabled or enhanced survival or, in pathological states, if it enhanced recovery or prolonged survival. In normal physiology, hibernation, with its zero food intake and negative energy balance, could be considered an appropriate control response to winter. In pathological states, there is indication that the reduction of food intake and consequent tissue depletion in infectious disease can improve the likelihood of recovery and so be appropriate (7). However, a process of this sort can only be thought of as appropriate and protective, if, on balance, it works. There is no evidence that the hypophagia and depletion of cancer in any way increase the likelihood of recovery. Whether enteral or parenteral supplementation of food intake or induction of increased voluntary intake increases survival time or improves condition in the absence of other treatment has never been investigated explicitly. In default of evidence to the contrary, we assume that the hypophagia and tissue depletion do not confer an advantage and are not protective, but it should be recognized that this is an assumption and not a self-evident truth.

If hypophagia is not appropriate control response to cancer, then the control of food intake is impaired. An obvious first possibility is that the hypothalamic feeding control system is involved. Either it fails to respond to true hunger signals due to functional impairment, or, undamaged, it responds to spurious signals generated by the tumor that mimic satiety. Damage to the ventromedial hypothalamus that produces the classical hyperphagia and obesity in normal rats and mice or during early (precachectic) tumor growth, or damage to the lateral hypothalamus that produces acute aphagia with later "escape" and chronic residual feeding deficits, do not in any way block or alter the development of tumor-induced hypophagia and cachexia (8–10). The amount of work on this has been small and relatively crude and does not cover a broad range of tumors. Nevertheless, the existing evidence is against any direct hypothalamic involvement in the impairment of feeding control in cancer.

There are a number of stimuli to which normal animals respond with predictable change in food intake and these responses reflect individual components of the total feeding control system. Over the past few years we have been examining the influence of tumor growth on changes in response to these stimuli: caloric density of food; environmental temperature; aversive taste adulteration; exogenous insulin; amino acid deficiency; and imposed exercise. So far, only the work on

response to caloric density of food has been completed and analyzed, (11,12), but there are preliminary data from our studies and data from other laboratories on some of the others.

The response of most mammals to caloric dilution of diet with nonnutritive bulk is to increase bulk intake to the point that nutrient intake is maintained at a constant level. This response holds in Sprague-Dawley (S-D) rats, with complete compensation up to 50%–60% dilution of a base diet supplying about 4.5 kcal/g (11). During the growth of Walker 256 carcinosarcoma (W256), this response starts to fall short of complete compensation in the first quarter of tumor life and is completely abolished by the last quarter (fig 2b) (11,12). However, there is no decline of food intake or overt cachexia on the standard diet until the third or fourth quarter of tumor life (fig 2a). This identifies one functional site of impairment of feeding control and, since the impairment occurs long before there is overt cachexia, it shows that the impairment is being compensated.

Cachexia and the associated hypophagia have always been regarded as characteristically late features of tumor growth. The time course of impairment of response to caloric density of food suggests that we should distinguish between the cachectic process and the cachectic consequence. The former may start right at the beginning of the cancerous process and be compensated and silent for most of its course. This also raises doubt about the valdity of the belief that some cancers are cachectic and some are not. It is possible that in the apparently rarely cachectic cancers the cachectic process is operative but is compensated long enough to allow the cancer to kill the host by other effects.

The normal (tumor-free) Buffalo (B) strain of rat does not show the feeding response to caloric density of food (fig 2b) (13). However, when the Morris 5123 hepatoma (H5123) is grown in rats of this strain, the normally zero response to caloric density is turned negative so that, rather than failing adequately to increase its food intake, this rat moves to a zero food intake of the dilute diet (fig 2b). Also, in this case, the impairment appears at or slightly after the first appearance of overt hypophagia, suggesting that there is at least one other component of feeding control already impaired and that, although response to caloric density is not normally actively expressed in this strain, it exerts a permissive feeding effect that can be damaged.

Some feeding response to reduced environmental temperature survives into the overt cachectic phase of tumor growth (14), but there are indications (14 and paper in preparation) that the response is distorted and attenuated. Feeding response to amino acid deficiency (15) and taste perception (16) are also distorted. All of these impairments occur at the beginning of or during the overt cachectic phase.

Information on feeding response of tumor-bearers to exogenous insulin is still preliminary, but both the S-D/W256 and the B/H5123 organisms appear to show a positive and qualitatively normal feeding response through most of tumor growth (fig 2c) (12). There is some indication that the response may be greater than normal in the middle of tumor life (fig 2c), suggesting that this response may contain part of the compensation for earlier deletion of other control components.

Some components of the feeding control system, then, are impaired by tumor growth and at least one is not impaired. Those responses that have been found to be impaired are all mediated predominantly extrahypothalamically (17,18). The one feeding response so far found that is unimpaired, response to exogenous insulin, is mediated predominantly hypothalamically (18). This gives added force to the earlier findings of noninvolvement of the hypothalamus in the development of cancer cachexia and should at least act as a caveat against too facile invocation of hypothalamic function in explaining cachectic phenomena.

COMPENSATION FOR IMPAIRMENT OF FEEDING CONTROL

The components of control that are impaired are impaired in succession rather than simultaneously. Also, the appearance of impairment of individual components of control long before there is detectable hypophagia or cachectic depletion shows that these early deficits are compensated. The normal, total feeding control system is multiple and highly redundant; individual components of control overlap and one or a few can be deleted from the total potential set without substantial interference with overall control. This is illustrated both by the absence of the caloric density response in B rats, and by the ability of "escaped" lateral rats to control their food intake quite effectively although the feeding response to insulin-induced celular glucopenia is now permanently deleted (18). It seems likely from the available information on impairment of feeding responses in tumor-bearing rats that the tumor successively deletes individual feeding controls. Initially, the redundancy of the total system permits compensation with no overt effect on food intake. Eventually, so many of the individual components are deleted that redundancy is lost, compensation is no longer possible, and effective control of food intake is lost.

Although it is possible that the feeding response to insulin plays a part in the proposed compensation process, it is unlikely that it plays an important part, since the insulin response is mediated hypothalamically and hypothalamic destruction does not affect the cachectic process. However, there is other evidence of early compensation. An animal can reduce its food intake in

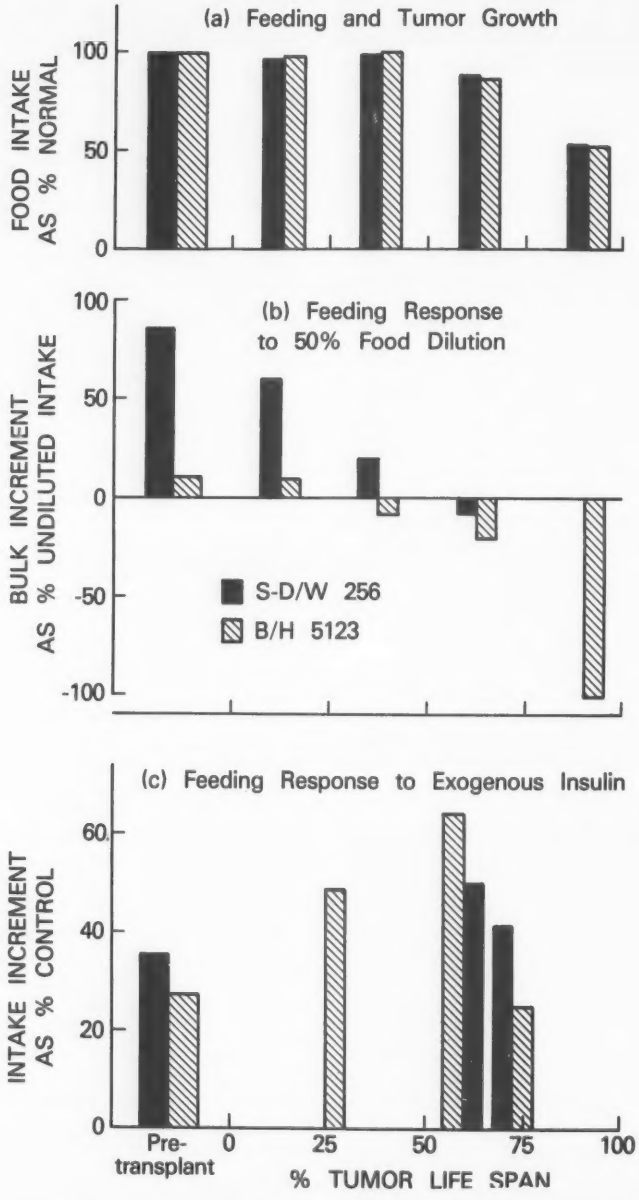

FIGURE 2.—The course of (a) decline of food intake, (b) deterioration of response to 50% caloric dilution of diet, and (c) response to exogenous insulin (1.5 U/100 g, protamine zinc insulin) of Sprague-Dawley rats growing Walker 256 carcinoma (S-D/W256)—*solid blocks*, and Buffalo rats growing Morris 5123 hepatoma (B/H5123)—*hatched blocks*. Growth of the tumors is expressed as fraction of life span of tumor (time from transplant to death of host from tumor). The absolute tumor life spans are: W256, 30 days; H5123, 50 days.

two ways: it can reduce the total amount of the feeding activity, or it can reduce its feeding efficiency, ie, the amount of food ingested per unit of feeding activity. For normal rats in a uniform environment eating a constant amount, the daily feeding activity and feeding efficiency are fairly constant (19). In three host/tumor organisms (S-D/W256, S-D/4M and B/H5123), the feeding activity starts to decline within the first half of tumor life. But the feeding efficiency increases correspondingly so that there is, for this period, no change in food intake. The feeding activity then continues to decline but the feeding efficiency falls or stops rising with resultant decrease in food intake in the second half of tumor life (20). Thus compensation is demonstrated in an external behavioral change. The existence of compensation reinforces the view that cancer hypophagia is not a protective mechanism. The underlying physiological mechanism of this change in feeding efficiency is unknown.

ASTHENIA AS A NONSPECIFIC CONSTRAINT ON FEEDING

Another important feature of cancer cachexia is asthenia (21). The analogue of clinical asthenia in experimental animal tumor systems is progressive depression of motor activity, which can be quantitatively demonstrated as the depression of the total amount of energy expended on motor activity (fig 1c,d) (22,23). Of four host/tumor organisms that have been examined in this respect, three show progressive depression of the energy compartment of motor activity (S-D/W256, S-D/4M and F/MCA-S) while one (B/H5123) shows no change in this compartment; but all show hypophagia and cachexia. Thus asthenia is frequent but unlike hypophagia is not an invariable concomitant of cachexia.

Feeding is a motor activity. The amount of motor activity that an animal engages in is not a control of feeding, but the capability for some minimum level of motor activity is a necessary condition for feeding. Feeding only occurs and can only occur during periods of motor arousal (24). In the S-D/W256 and S-D/4M organisms decline of food intake is linearly correlated with decline of motor activity (23), so that even moderate constraint on the capability for activity can constrain feeding. When periods of motor arousal no longer exist, as is finally the case in the three host/tumor organisms cited, feeding cannot occur even if sufficient remnants of the specific feeding control mechanism still formally survive. Thus, asthenia can eventually override all other mechanisms in preventing feeding. Indeed, loss of capability for motor activity disables all control systems that involve external behavior as a link in the process.

In normal rats in a constant environment, the activity compartment of total energy expenditure is very constant and is unaffected by body weight or by imposed food restriction or depriva n (24). Also, in the F/MCA-S organism, maintenance of nutrient input by total parenteral nutrition can maintain body weight and positive energy balance but does not prevent or reverse the development of asthenia (25). The asthenia is not, therefore, a secondary effect of already reduced body weight and food intake.

CONCLUSIONS AND QUESTIONS

The variability in course of development of hypophagia and cachexia is a function of the timing and sequence of deletion of individual feeding controls, the capacity for compensation for deleted controls, and the occurrence and timing of the overriding asthenia. The tumorous organism in which there is no asthenia (B/H5123) has the slowest and most uniform development of hypophagia and cachexia (fig 1f). However, the overriding effect of asthenia raises questions concerning the interpretation of the apparent response of specific feeding controls when these show impairment during the asthenic phase.

Since the asthenia disables the expression of all feeding controls, is the apparent impairment of controls late in tumor life simply a reflection of the asthenia? In the case of insulin, does the maintained feeding response in late tumor life indicate a different response mode from the normal? For the B/H5123 organism, which shows no asthenia, the insulin could induce feeding by the same mechanism as in the tumor-free rat. But in the S-D/W256 organism the insulin must, presumably, first restore motor activity before the normal response mechanism could be effective. Can the hyperphagic response to insulin be evoked after asthenia has fully developed? We know that restoration of nutrient input will not restore motor activity, but would restoration of motor activity restore voluntary food intake? At present there are no answers to any of these questions.

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A Central Mechanism for Anorexia in Cancer: A Hypothesis[1]

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Starvation and progressive depletion in patients with neoplastic disease is being recognized increasingly as a clinical problem that seriously interferes with therapeutic possibilities. The starvation and loss of lean body mass and the associated decrease in host resistance, to either the point of anergy to delayed recall antigens, not only may favor a malignant growth (1) but the associated decrease in nonspecific host resistance may leave the patient open to invasion by opportunistic infection (2,3).

There has been a tendency to think of the weight loss and pronounced depletion as a symptom of advanced malignancy, where presumably the needs of the extensive tumor burden take precedence of that of the host and the host starves so the tumor may grow. Recent work, however, has shown that this may be a relatively early phenomenon before tumor burden is significant (4). Thus interest in "cancer cachexia" as being either humorally mediated or involving a central mechanism has increased recently, with increasing speculation concerning deranged physiological mechanisms that normally regulate feeding behavior. We suggest here that the central serotonergic system, which may play an important role in controlling food intake in general, is particularly deranged in neoplastic disease and may be responsible, at least in part, for the emergence of cancer anorexia. A few words concerning the control of feeding behaviors seem appropriate at the present time.

PHYSIOLOGY OF FEEDING BEHAVIOR

Classical neurophysiological experiments have identified "centers" for "feeding" and "satiety" within the hypothalamus. Animals with experimental hypothalamic lesions are widely used as models of hypo- or hyperphagia depending on whether the lesion is in the ventrolateral or ventromedial hypothalamus respectively (5,6). Stimulation of feeding activity also results from involvement of the catecholaminergic system in the paraventricular nucleus of the hypothalamus (7). What has not been known heretofore is how this catecholaminergic system is linked to parameters that are derived from the consumption of food. In 1956, Mellinkoff (8) proposed a relationship between peripheral plasma amino acid levels and appetite. It has gradually become clear over the past decade that plasma amino acid concentrations influence levels of brain amino acids and thus changes in plasma amino acids do influence neurotransmitter synthesis by the availability of precursor amino acids (9).

Nevertheless, relating dietary input to hypothalamic catecholaminergic activity is difficult, in part because tyrosine hydroxylase, the rate-limiting step of catecholamine synthesis, is responsive to end-product inhibition and other controls that reflect variations in neuronal activity. Thus plasma amino acids alone would be unlikely to regulate catecholamine synthesis and produce the necessary changes in feeding behavior, unless neuronal modification utilizing another system that depends on feeding behavior influences catecholamine activity.

Serotonin and the serotonergic system appear good candidates for this hypothetical intermediary. To begin with, the hypothalamus contains a large number of serotonergic nerves. The neurons originate in the phylogenetically older midline raphe nuclei of the midbrain and the brain stem (10–12). Furthermore, the rate of serotonin synthesis in these systems is closely related to precursor availability and to general nutritional status.

The rate-limiting enzyme of conversion of tryptophan to serotonin is unsaturated at normal brain tryptophan levels (fig 1). Thus brain tryptophan levels more or less regulate the available neurotransmitter within the central nervous system. It is not our purpose here to become involved in the debate concerning the penetration of tryptophan across the blood-brain barrier. Suffice it to say that at least three factors are involved: the concentration of plasma free tryptophan (13,14) (plasma tryptophan unbound to albumin, its normal carrier); the molar ratio of tryptophan as compared with the other neutral amino acids in plasma that compete for tryptophan for transport across the

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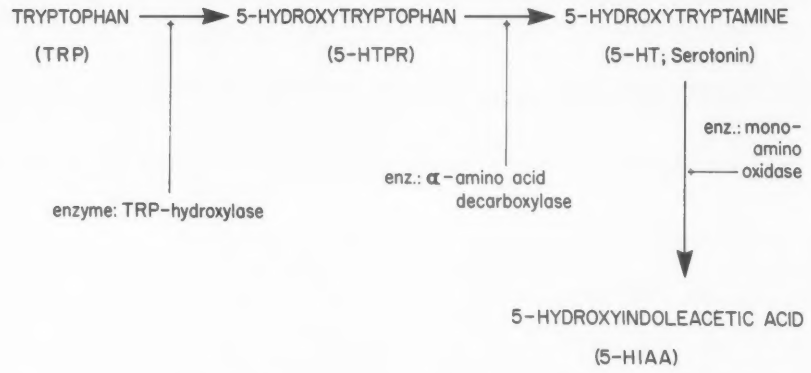

FIGURE 1.—Scheme of metabolic pathway of central tryptophan to serotonin and 5-hydroxyindoleacetic acid. At physiologic concentrations of tryptophan, tryptophanhydroxylase is unsaturated, thus rendering the concentration of this amino acid rate-limiting in the process of synthesis and metabolism of serotonin. The concentrations of the 5-HT metabolite, 5-HIAA, reveals alterations in serotonin turnover more readily than 5-HT levels do.

blood-brain barrier (15); and the brain uptake index of tryptophan, a characteristic of the transport system itself in carrying tryptophan from the plasma into the brain (16).

Ingestion of carbohydrate, for example, causes plasma tryptophan, brain tryptophan, and consequently serotonin to increase as a result of the decrease in the branched-chain amino acids under the influence of insulin and possibly displacement of tryptophan from albumin because of changes in plasma nonesterified fatty acids. Protein intake may also, in part, regulate plasma and brain tryptophan concentrations. Under normal circumstances, at least in rats, diets are selected to keep the ratio of plasma tryptophan to the sum of neutral amino acids constant (17). When such a choice is not available to an animal, plasma tryptophan concentrations will vary. Tryptophan-deficient diets cause lower plasma and brain tryptophan concentrations, as does malnutrition (18,19). In like manner, the consumption of dietary fats by increasing plasma nonesterified fatty acids also increases brain tryptophan by displacing tryptophan from albumin, making it more easily available for uptake into the brain (20).

Additional evidence implicates serotonin in feeding behavior. Direct injection of serotonin into the ventricles of the brain results in anorexia (21). Various drugs that increase brain tryptophan concentrations indirectly also result in anorexia. Examples are fenfluramine (22) and fluoxetine. Pretreatment with serotonin precursors (tryptophan or 5-hydroxytryptophan) enhances the anorectic action of these drugs.

Reduction in brain serotonin stimulates appetite. Inhibition of serotonin synthesis by parachlorophenylalanine, or the use of serotonin receptor blockers such as methysurgide or cyprohetadine, abolishes the anorectic effect of serotoninergic drugs and by themselves cause hyperphagia in rodents, cats, and humans (23–33).

HYPOTHESIS

We propose that anorexia in tumor-bearing animals is the direct result of abnormal central serotonin metabolism (34), and that this derangement in central nervous system serotonin metabolism may result in cancer-related anorexia in man.

In a recent study (34) we compared three groups of matched young (90-100 g) Sprague-Dawley rats. One group received an implantation of 10^6 Walker 246 carcinosarcoma cells, and was allowed free access to food and water. Two additional groups were sham-injected with saline. One group was pair-fed, ie, received the same quantity of food consumed on the previous day by its paired tumor-bearing rat. The third group (also saline-injected) was allowed free access to food. The use of these three groups made it possible to differentiate between "tumor specific" effects and those due to a reduced dietary intake. Within 10 days, the food intake in the tumor-bearing rats (and hence in their pair-fed controls) had fallen significantly behind that of the free-feeding rats. Analysis of the factors influencing serotonin metabolism in the tumor-bearing and pair-fed rats at this time showed brain tryptophan levels were significantly higher in the tumor rats, and brain serotonin turnover, as indicated by levels of its metabolic product 5-HIAA (table 1), was proportionally increased.

TABLE 1.—Brain TRP, 5-HIAA, and 5-HT values in three groups of rats (mean±SEM)*

	TB	PF	FF
Brain TRP (nmol/g)	27.15 ± 2.40†	18.60 ± 1.40	19.80 ± 0.55
5-HIAA (pmol/g)	1.888 ± 0.152†	1.433 ± 0.84	1.553 ± 0.110
5-HT (pmol/g)	3.019 ± 0.136‡	2.852 ± 0.114	2.747 ± 0.159

Tumor-bearing rats were implanted with 10^6 carcinosarcoma cells. Anorexia supervened on approximately Days 2-5, and at the end of Day 9, when the animals were killed, oral intake had been 20% less than the control animals for at least 72 hours. Pair-feeding was carried out in litter mates injected with saline by giving the amount of food that had been consumed the previous 24 hours. The results show that the brain tryptophan is clearly increased in tumor-bearing rats, as is 5-hydroxyindoleacetic acid (From ref 48.)

*$P < 0.05$
†$P < 0.01$
‡Not significant

Although plasma total tryptophan concentrations were decreased in both groups, the concentration of plasma free tryptophan was significantly higher in the tumor-bearing rats (fig 2a). This was due to a decrease in binding of tryptophan to albumin, a consequence of raised plasma concentrations of nonesterified fatty acids and decreased plasma albumin concentrations. Other factors known to influence brain uptake of tryptophan were the same in all three groups, thus confirming the widely held concept that the plasma free tryptophan concentration was the most important determinant of brain levels of tryptophan and serotonin (fig 2b) (20). The results also suggest that the decreased food intake of the tumor-bearing rats may be secondary to increased central serotonergic activity. Possible involvement of a catecholamine mechanism could not be ruled out as increases in brain tyrosine concentrations were also found in the tumor rats. However, this was also the case in the pair-fed rats, suggesting that it might be the result rather than the cause of the low food intake (34). Furthermore, in keeping with the relative independence of catecholamine synthesis upon precursor levels, despite the increase in tyrosine concentration within the brain, catecholamine levels were not significantly elevated (fig 2c).

One of the other mechanisms that might possibly influence the penetration of tryptophan across the blood brain barrier, and perhaps increase or decrease brain serotonin and thus influence behavior, is the relationship between the molar concentrations of other plasma neutral amino acids, those that normally compete with tryptophan for entry across the blood-brain barrier. Therefore, in another series of experiments plasma and brain amino acids were measured in three similar groups of rats: saline-injected controls, freely feeding rats implanted with tumor cells which subsequently become anorectic, and saline-injected pair-fed animals. It was not possible to explain the increase in brain serotonin by decreased competition at the blood brain barrier by the other neutral amino acids (34). Thus it seems likely that to a significant extent, at least in the animal model, the decrease in nutritional uptake in rats implanted with tumors appeared to correlate directly with increased brain concentrations of tryptophan, in turn secondary to displacement of tryptophan from albumin by increased nonesterified fatty acid.

ATTEMPTS TO LOWER BRAIN TRYPTOPHAN

The controlling influences concerning uptake of tryptophan across the blood brain barrier are rather well known and it should be possible to manipulate the concentration of brain tryptophan by a number of maneuvers. These include:

1) Decreasing free tryptophan within the plasma; this may be accomplished by increasing plasma albumin, binding tryptophan and making it less available for transport across the blood-brain barrier;
2) Decreasing free fatty acids; the administration of hypertonic glucose, which will both decrease glucagon and also inhibit lipolysis secondary to insulin, will also result in decreased plasma free tryptophan thus making it less available for transport across the blood-brain barrier;
3) Increasing the branched-chain amino acids, which provide the bulk of the competition for tryptophan within the neutral amino acid group for penetration across the blood-brain barrier.

All of these are applicable. It is by far easiest in the clinical situation to increase the branched-chain amino acids within the diet and thus in the plasma, to compete with tryptophan for entry across the blood-brain barrier.

The next series of experiments were undertaken with the same animal model, ie, rats implanted with tumors which normally could be expected to become anorectic over 5-9 days following tumor implantation. One

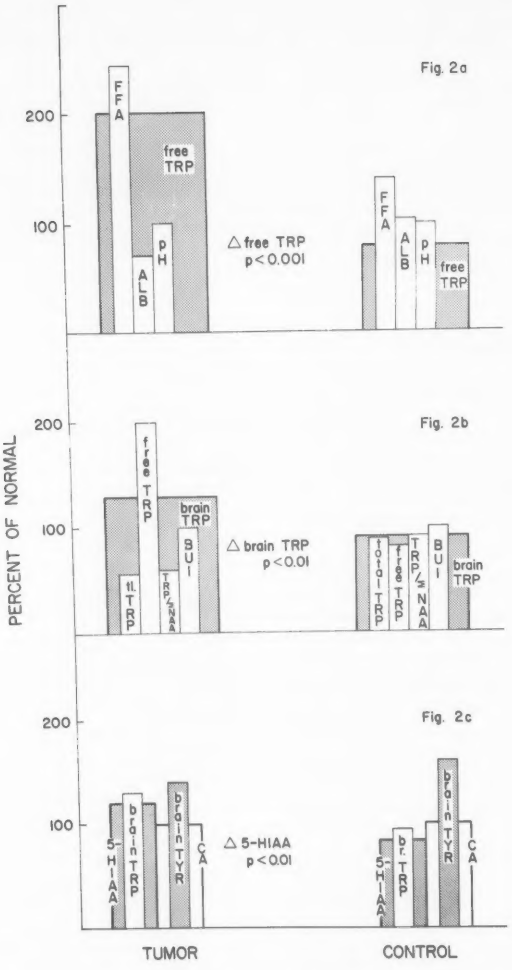

FIGURE 2a.—Relative plasma free tryptophan (TRP) levels expressed as percentage of mean values determined in a freely feeding, nontumor-bearing control group. In figures 2a, b and c, tumor-bearing rats are compared with a group of pair-fed, tumor-free control group. The large shaded columns represent free tryptophan values (%) and the narrow, unshaded columns represent the relative concentrations (%) of the major determinants of plasma free TRP: free fatty acids (FFA), albumin (Alb), and pH.

FIGURE 2b.—Relative brain tryptophan (TRP) concentrations (%) in the same groups as referred to in figure 2a. The large, shaded columns represent brain tryptophan concentrations (%). The narrow, unshaded columns refer to the major determinants of brain TRP concentrations: total TRP = total tryptophan in plasma: TRP/ΣNAA = ratio of plasma TRP to the sum of the competing neutral amino acids: BUI = brain uptake index for tryptophan as determined with the method of Oldendorf (*see* ref 23).

FIGURE 2c.—Relative concentrations in the brain (%) of 5-hydroxindoleacetic acid (5-HIAA; large, shaded columns) and catecholamines (CA; large, unshaded columns) both expressed in their relation to the concentrations (%) of their respective precursor amino acid: tryptophan (TRP; narrow, unshaded column) for 5-HIAA and tyrosine (TYR; narrow, shaded column) for catecholamines. The same groups are considered here as mentioned above. Statistics are based upon Student's t-test for paired data.

group was maintained on normal animal chow and the other group was maintained on a branched-chain-enriched amino acid diet. One must be very careful in performing such dietary studies since animals will often not eat diets that are slightly abnormal, are imbalanced, or do not contain all of the essential nutritional elements. However, it was possible to manufacture such a diet to the appropriate taste so animals would not decrease their intake when confronted with it (fig 3). The results of these experiments suggest that the emergence of neoplasm-related anorexia is delayed by the administration of a branched-chain-enriched amino acid diet. Preliminary studies on the plasma and brain amino acid concentrations suggest that the penetration of tryptophan and brain serotonin was in fact decreased when appetite was maintained and that the desired effect was achieved.

STUDIES IN PATIENTS

It is obviously difficult to obtain similar data from anorectic cancer patients but it is known in man that brain tryptophan levels correlate well with serotonin activity. If one accepts the premise that plasma free tryptophan is as important in determining brain concentrations in man as in a tumor-bearing rat, indirect evidence for increased brain serotonin activity might be inferred from increased plasma free tryptophan concentrations. In the plasma of patients with presumably cancer-related anorexia, we have found similar changes in the distribution of plasma tryptophan with a marked increased in the free tryptophan component. This also appears secondary to increased nonesterified fatty acids within the plasma (fig 4).

It should follow, therefore, that therapeutic manipulation of plasma free tryptophan levels in man by the administration of hypertonic dextrose might paradoxically increase appetite or administration of oral branched chain amino acids might also result in increased appetite.

We have initated such therapy in patients with the anorexia of cancer and the results are very encouraging. This hypothesis, suggesting a role of a serotoninergic system in regulating normal feeding behavior in man, and the suggestion that derangements in this system may explain cancer anorexia, are exciting but clearly preliminary and far from proven. Neuropharmacological manipulation of normal and tumor-bearing

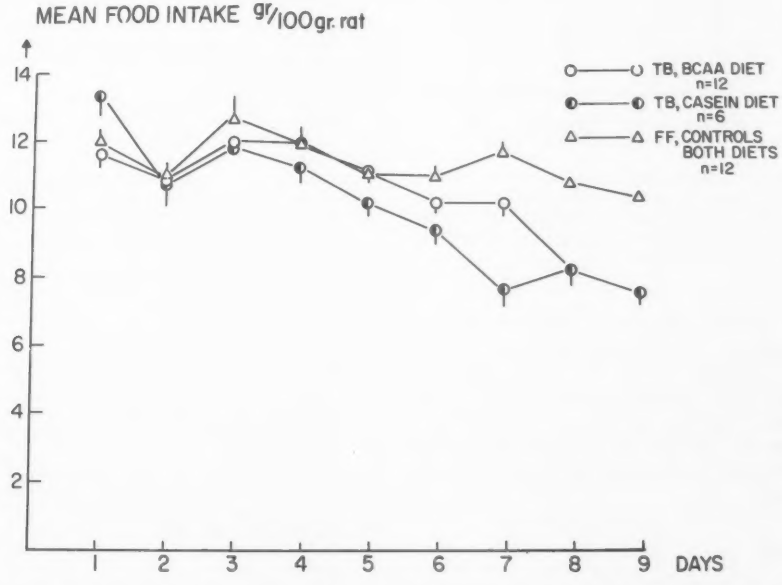

FIGURE 3.—Rats with implanted tumors as described in the text were maintained on either casein diet or casein diet with added branched-chain amino acids. Note, too, that the onset of anorexia is delayed by 2 days in the group receiving the high branched-chain diet. There are no statistically significant differences in intake between the tumor bearing group on the BCAA diet and the freely feeding controls for the sixth and seventh days, whereas there is a statistically significant difference between the tumor bearing group on the casein diet and the freely feeding group for both Days 6 and 7.

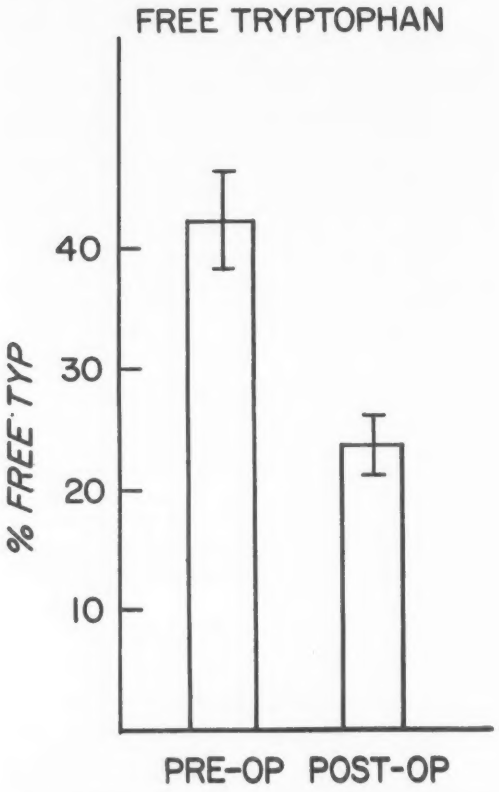

FIGURE 4.—Percentage of free tryptophan in patients with tumors preoperatively and following resection. These patients have slightly evlevated free fatty acids, displacing tryptophan from plasma. The results suggest that the mechanism in experimental animals may very well operate in patients as well.

animals may provide additional supportive evidence. In the final analysis, however, only success in clinical practice will be the final arbiter. If this hypothesis is even partially correct, cancer anorexia may be treatable by pharmacological manipulation of plasma tryptophan and the factors that influence the penetration and concentration of brain tryptophan and the serotoninergic system.

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Animal Models for the Study of Cancer-Induced Anorexia[1]

S. Garattini[2,*] and A. Guaitani[2,3]

SUMMARY

Walker carcinoma 256/B transplanted sc in CD-COBS rats induce a decrease of food intake when the tumor size is less than 5% of the body weight. This anorexia is accompanied by a decrease of the adipose tissue and, to a lesser extent, of muscular tissue. The mechanism involved in cancer-induced anorexia seems to be different from that of classic centrally acting anorectic agents. Among the drugs tested to counteract this anorexia only cyproheptadine shows a modest effect. Cyclophosphamide reduces tumor growth and prevents decrease in food intake. It is suggested that Walker carcinoma 256/B may be a useful animal model to study problems related to cancer-induced anorexia and cachexia.

[Cancer Treat Rep 65 (Suppl 5):23-35, 1981]

It is well known that cancer patients suffer anorexia and that the consequent decrease in food intake contributes to the cachexia characteristic of the malignant neoplastic diseases. The degree of anorexia and cachexia varies widely in relation to the type and localization of the malignancy (1,2). The causes of anorexia and cachexia are poorly understood and the origins may be multiple. Several reviews have summarized current knowledge in this field showing that the reasons for these symptoms include taste alterations (3,4), release of toxic material from the tumor (5,6), and imbalance of nutrients (7-12).

It is obvious that anorexia and cachexia contribute to lowering the host's defenses against tumor growth and that any effective means of counteracting these symptoms could be of benefit to cancer patients.

The availability of animal models for the study of cancer-induced anorexia and cachexia could be of value in developing new drugs or in testing drugs with anabolic or orexigenic (appetite-increasing) activity, and in elucidating the mechanisms responsible for these symptoms. Several attempts have been made in the past to develop animal models for this purpose but their application in the study of new drugs has been very rare. Furthermore, these models lacked a quantitative approach in their development.

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[3]We thank Cristina Pintus and Giovanna Piccinelli for their skillful assistance.

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SUMMARY OF THE EXISTING ANIMAL MODELS TO STUDY TUMOR-INDUCED ANOREXIA

This section is restricted only to experimental observations based on a direct approach to the problem. In other words, information such as amounts of food eaten by tumor-bearing animals has little value unless the relationship between the food intake, the weight of the host, and the development of the tumor is clearly specified. A complicating factor in the evaluation of such data is the scant information available on the composition and constancy of the diet given to laboratory animals. It should be added that the information available to date is mostly limited to tumors growing in rodents (mice and rats). Unfortunately, any generalization is impossible because every combination of a given tumor growing in a given strain of a given animal species seems to result in a unique model where the anorexia-cachexia shows a different degree of severity and, in some instances, even peculiar mechanisms. An additional obstacle is that, in the old literature in particular, but in recent works too, it is often difficult to extrapolate data from one laboratory to another because the tumors may come from a transplantable line that has lost or gained given biological characteristics.

With these limitations, table 1 summarizes a number of findings reported in the literature concerning changes of food intake in tumor-bearing rats. The data

TABLE 1.—Reduction of food intake in tumor bearing rats

Strain of rats	Tumor	Site of growth	Diet	Time of observation (days)	Tumor weight (g)	Decrease in food intake (%)	References
Wistar	Walker 256	sc	Casein, glucose, Crisco	50-60	50	> 50	15
Sprague-Dawley	Walker 256	sc	ALAL	21	42	> 50	11
Sprague-Dawley	Walker 256	sc	Casein-semi-synthetic	28	75	< 50	13
Sprague-Dawley	Walker 256	sc	Standard diet	21	50	< 50	16
Sprague-Dawley	Walker 256	sc	Diluted diet	21	50	> 50	16
Sprague-Dawley	4 M mammary ca	sc	Casein-semi-synthetic	28	50	< 50	13
Sprague-Dawley	T8 Guerin	sc	ALAL	21	65	< 50	11
Sprague-Dawley	Flexner-Jobling	sc	ALAL	21	12	NC*	11
Buffalo	Morris hepatoma 5123	sc	Casein-semi-synthetic	28	10	< 50	13
M520xAXC9935	Dunning lympho-sarcoma R 2788	sc	NCI	21	52	NC	14
M520xAXC9935	Morris hepatoma 3683	sc	NCI	32	33	< 50	14

*NC = no change compared to controls.

are not completely comparable because the strains of rats and the diets utilized are additional variables as well as the strains of tumor considered. However, a few considerations are possible:

(*a*) The majority of experimental tumors induce a marked decrease of food intake in the host. The effect is not transplant-related, since animals implanted with nongrowing tissues such as muscle or liver do not show anorexia (13);

(*b*) The absolute weight of tumor does not seem to be of importance in determining the presence of anorexia. For instance, the Dunning lymphosarcoma R 2788 growing sc in rats M520 x AXC 9935 could reach a weight of over 50 g without causing any depression of food intake, while the Morris hepatoma 3683 growing under the same experimental conditions already depressed food intake when the tumor weighed only a few grams (14);

(*c*) The same tumor (eg Walker carcinosarcoma 256) may have a widely-varying effect, producing more (11,13,15) or less (16) anorexia. This shows that not all strains of Walker 256 are comparable; in fact, it is possible to derive lines with different biological properties from the same Walker 256 (17);

(*d*) The composition of the diet may have a key role in revealing anorexia in tumor-bearing animals; for instance, a diet diluted with nonnutrient bulk showed up anorexia induced by Walker 256 earlier and to a greater extent than a standard casein-based semisynthetic diet (16);

(*e*) When food intake is measured in individual tumor-bearing animals in the same group, some animals may have depressed food intake while others still show normal food consumption. This is the case of the 4M mammary carcinoma growing in Sprague-Dawley rats; the difference seems to be related more to the rate of growth than to the absolute weight of the tumor (13).

Food intake in tumor-bearing mice has been studied less, probably for technical reasons due to the difficulty of measuring small food consumption. Liebelt et al (18) have reported that the stomach tumor 2663 syngeneic in CBA mice can reach the size of one 1 without causing any decrease in food intake, anorexia occurring only in moribund animals. However, when this tumor was transplanted in the same strain of mice made obese by gold thioglucose or in genetically obese (CBA x YBR) F_1 hybrid hosts, there was a marked loss of body weight accompanied by a fall in food intake. Certain tumors are known to elicit anorexia in obese animals.

In the same hybrid host ($C_{57}B1$ x CBA)F_1, the stomach tumor 2663 induces a marked decrease of food intake one week after transplantation while sarcoma 14 (originated in $C_{57}B1$ mice) has little such effect even 30 days after transplantation (18).

The Lewis lung carcinoma (3LL), a highly metastasizing tumor syngeneic in $C_{57}B1/6$ mice, has been studied in some detail in our laboratory. Figure 1 summarizes data concerning the relationship between tumor growth in $B_6C_3F_1$ inbred mice and changes of body weight and food intake[4]. With this tumor, weight

[4]M.G. Donelli, unpublished data.

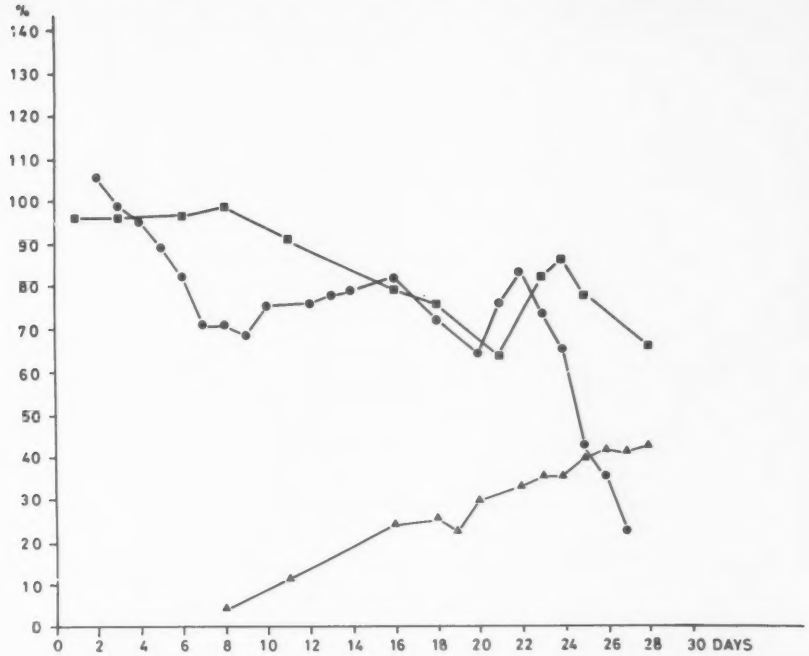

FIGURE 1.—■———■ Body weight (net of tumor) as percent of controls ●———● Food intake as percent of controls ▲ – – – ▲ Tumor weight as percent of body weight of Lewis Lung carcinoma (3 LL) bearing $B_6C_3F_1$ mice.

loss starts around 17 days after tumor transplantation when food intake is only moderately reduced. A 50% decrease in food consumption is seen only when the animals are almost moribund and when the tumor weight amounts to almost half the body weight.

THE USE OF WALKER CARCINOSARCOMA 256

Fragments of 100 mg of proliferating Walker carcinoma 256/B[5] obtained from donor animals 11 days after transplantation, were implanted sc on the right-hand side in the scapular region of CD-COBS male rats (Charles River, Italy) 6 weeks of age, and weighing 140±2 g. Information about housing and other technical details are reported elsewhere (19).

As set out in figure 2, after a lag period of 4 days the tumor becomes palpable and starts to grow very rapidly, reaching a weight of 40 g around the 14th day after transplantation. When the tumor is around 5 g (6th day) the total (with tumor) and the net (without tumor) body weights start to fall below the weight of sham-operated animals. Beginning on the same day there is also a marked drop in food intake, which continues till the death of the animals (see fig 3). It is thus legitimate to ask whether the fall in food intake as responsible for the loss of body weight. The use of pair-fed animals (animals receiving the same food intake of the tumor bearing animals, the following day) indicates, however, that anorexia only partially explains the loss of body weight as also shown in figure 3.

The loss of body weight involves both tissues rich in lipids (adipose tissue) and in proteins (muscles). Epididymal adipose tissue, taken as representative of white adipose tissue, begins to decline on the 8th day after tumor transplantation, and weighs less than 5% of the epididymal adipose tissue of control animals at death. As shown in figure 4, panel 1, pair-fed animals also show a loss of epididymal adipose tissue but to a much lesser extent than in tumor-bearing rats. The drop of adipose tissue weight is consistent with previous observations indicating lipid mobilization from adipose tissue (increase of circulating free fatty acids) in relation to tumor growth, probably related to the release of

[5]Kindly supplied by Dr. Gericke, Hoechst, Frankfurt/Main, West Germany.

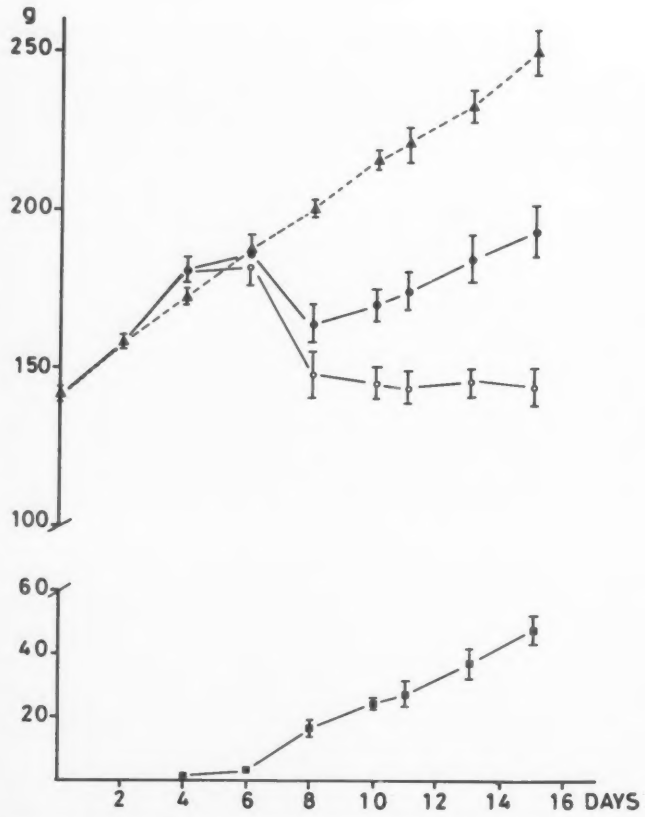

FIGURE 2.—Rats bearing Walker carcinosarcoma 256/B: ●——● total body weight of W56/B, ○——○ net body weight of W 256/B; ▲——▲ body weight of controls, ■——■ tumor weight.

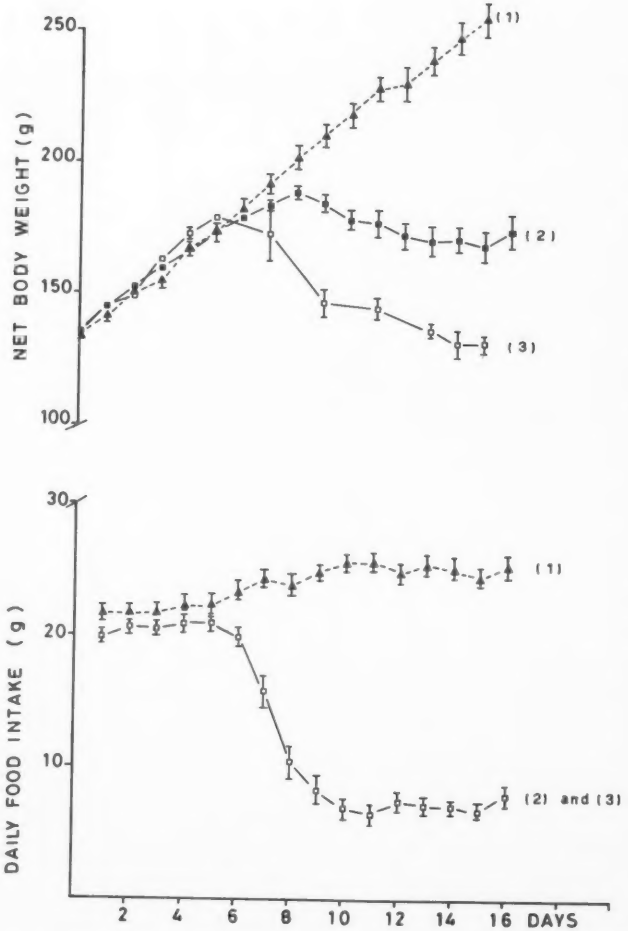

FIGURE 3.—Body weight and food intake of rats bearing Walker carcinosarcoma 256/B compared to ad libitum and pair-fed controls: (1) sham operated, (2) pair-fed animals, (3) W 256/B bearing rats.

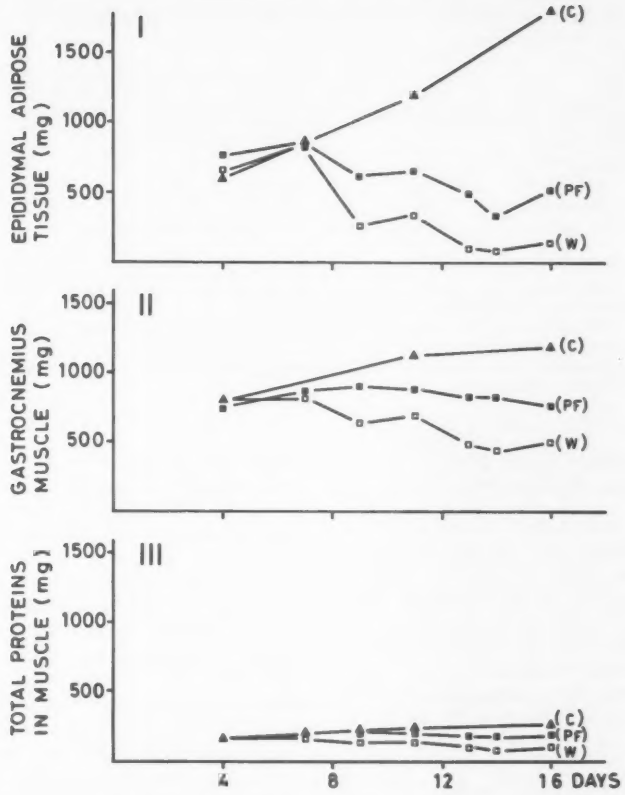

FIGURE 4.—▲——▲ sham operated controls, (c) □——□ W 256/B-bearing rats, (w) ■——■ pair-fed animals (PF) Statistical significance (I) = NS at Day 4; NS W ≠ PF, $P < 0.01$; W≠C and PF ≠ C at Days 9-11; $P < 0.05$ W ≠ PF, $P < 0.01$ W≠C and PF ≠ C at Day 16. (II) = NS at Days 4 and 7; $P < 0.01$ W ≠ PF at Day 9; $P < 0.01$ W ≠ PF, W ≠ C, PF ≠ C at Days 11,13,14,16. (III) = $P < 0.01$ W ≠ PF from Day 9 until Day 16.

tumor material with lipid-mobilizing activity (11). The results suggest that the animals die when no more energy-giving material can be obtained from adipose tissue to sustain host vital functions, since food intake is insufficient.

The gastrocnemius muscle, taken as representative of muscle tissues, also decreases in weight and in protein content in relation to tumor growth, but at much slower rate than adipose tissue (see fig 4, panel 2.) Pair-fed animals also show a loss in weight and protein content of gastrocnemius muscle but much less than the Walker 256/B-bearing animals.

It can therefore be established that Walker 256/B tumor-bearing animals very rapidly become anorectic when the tumor weight is about 3% of body weight. Since the tumor weight is too low to disable the animals or to mechanically affect the procurement of food it is suggested that the anorexic effect may depend upon release of toxic materials from the tumor mass. To compensate for inadequate food intake animals mobilize lipids from their adipose tissue and, to a lesser extent, proteins from muscles. Since the amount of lipids or proteins mobilized in tumor-bearing animals is greater than in control animals receiving the same amount of food, it is suggested that lipid or protein mobilization is induced not only by the condition of relative fasting but also by other mechanisms, including material released from the tumor.

The described model of tumor-induced anorexia and cachexia is reproducible, and is therefore suitable for testing drugs affecting food intake. The short survival time may also be an advantage for drug screening purposes. The reproducibility of this test under our experimental conditions is shown in table 2.

TABLE 2.—Hypothesis of the variables considered in assessing reproducibility

Variables	Total variation (= 100)		P value	Reproducibility between experiments
	Within experiments (%)	Between experiments (%)		
Body weight*	97.4	2.6	NS	+
Tumor:				
Max diam.*	89.3	10.7	NS	+
Min diam.†	63.6	36.4	< 0.01	−
Circumference†	67.3	32.7	< 0.01	−
Food intake*	89.5	10.5	NS	+

*Body weight, tumor maximum diameter, and food intake are the variables that should prove reproducible in future experiments.

†Tumor minimum diameter and circumference can be expected to vary from one experiment to another.

P value = level of significance; NS = not statistically significant; + = reproducible; − = not reproducible.

COMPARISON OF TWO LINES OF WALKER CARCINOSARCOMA 256

Different lines of the same tumor may behave differently as regards anorexia and cachexia. A line of Walker carcinosarcoma called here 256/A, received from Dr. I. Woodinsky (A.D. Little, Cambridge, MA), behaves quite differently from the line previously described, as shown in figure 5. This tumor line shows much slower tumor growth with a smaller loss of body weight, and food intake never decreases more than 50% in respect to controls even when the tumor accounts for a large percentage (40%) of the host's body weight.

Table 3 summarizes some of the characteristics of the two lines of Walker carcinosarcoma 256. Animals with line 256/A, in comparison with line 256/B, have a longer mean survival time, a larger net body weight, and a higher tumor weight at death. Histologically, line 256/B contained well-structured epithelial cells in the tumor mass with a large percentage of mitotic figures. No invasion of surrounding tissues was seen. The areas of epithelial growth were surrounded by areas in which cells became loose, rounded-up, and pyknotic with karyolysis and necrotic areas. Line 256/A showed a compact tumor mass with cells adhering to each other; there were few mitoses and necrotic areas were easily distinguishable from growing tissue.[6]

Representative microscopic pictures of the two lines are shown in figure 6.

A comparison was made by measuring anorexia and cachexia when the two lines of Walker carcinosarcoma 256 reached the same weight (around 20 g) at Day 9 after transplantation for line 256/B and Day 14 for line 256/A. Table 4 shows that at equal tumor weight animals with line 256/B have less epididymal adipose tissue and lower gastrocnemius muscle weight. In addition, line 256/B shows more marked leucocytosis than line 256/A and more severely damaged renal function, as shown by a lower urinary volume and reduced creatinine clearance (table 4).

It is interesting to recall that previous studies from this laboratory showed that the growth of several tumors impairs the activity of liver microsomal enzymes involved in the metabolism (hydroxylation, demethylation, nitroreduction, etc.) of foreign and endogenous compounds (20,21). Comparison of the two lines shows that 256/B impairs pentobarbital hydroxylation in vitro and in vivo to a greater extent than line 256/A (17). Whether the factor(s) involved in the inhibition of liver microsomal enzymes have any link with those causing anorexia is for the moment only a matter for speculation.

THE EFFECT OF AGENTS KNOWN TO INCREASE FOOD INTAKE

The model of Walker carcinosarcoma 256/B was utilized to investigate whether there are compounds which counteract anorexia in the host animals. The literature concerning orexic agents (compounds that increase appetite) is relatively scarce, as it is difficult to assess these compounds in laboratory animals. Nevertheless, a list of agents increasing food intake in some experimental conditions could be collected and is presented in table 5. Different doses and schedules of treatment were used, mainly with negative results as regards oxazepam, aminoguanidine, methergoline, and amitryptiline. However, as indicated in table 6, encouraging results were obtained with the use of cyproheptadine. This agent at certain doses did have some effect in increasing food intake and body weight in tumor-bearing animals. The fact that the effect is limited to certain doses indicates that the problem

[6]L. Morasco, unpublished data.

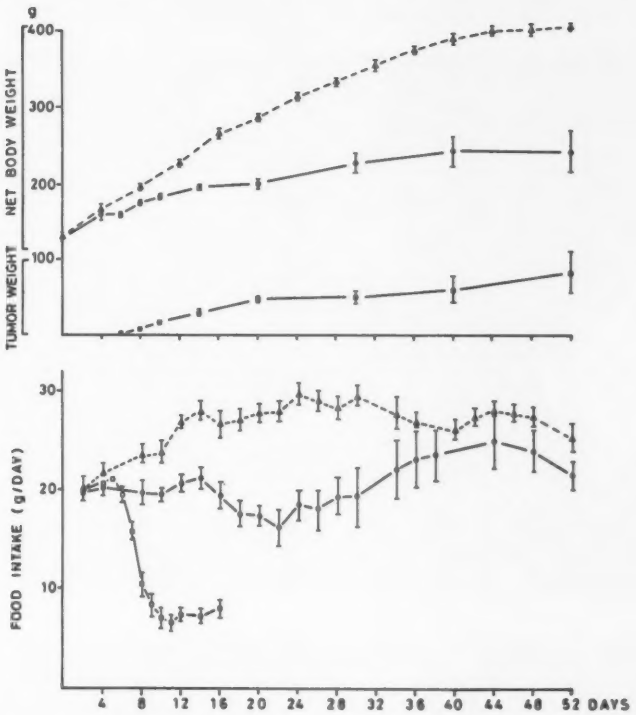

FIGURE 5.—Rats bearing Walker carcinosarcoma 256/A: ●——● net body weight and food intake of W 256/A ▲------▲ body weight and food intake of controls ■——■ tumor weight □——□ food intake of W 256/B.

TABLE 3.—Characteristics of two lines of Walker carcinosarcoma 256 growing in CD-COBS rats

Parameter	W 256/A	W 256/B
Mean survival time (days ± SE)	27 ± 1.5	14 ± 1
Net body weight* (g ± SE)	175.0 ± 6.1	128.2 ± 2.0
Tumor weight* (g ± SE)	70.8 ± 5.0	39.6 ± 1.7
Tumor (% body weight)	40.5	30.9

*At death.

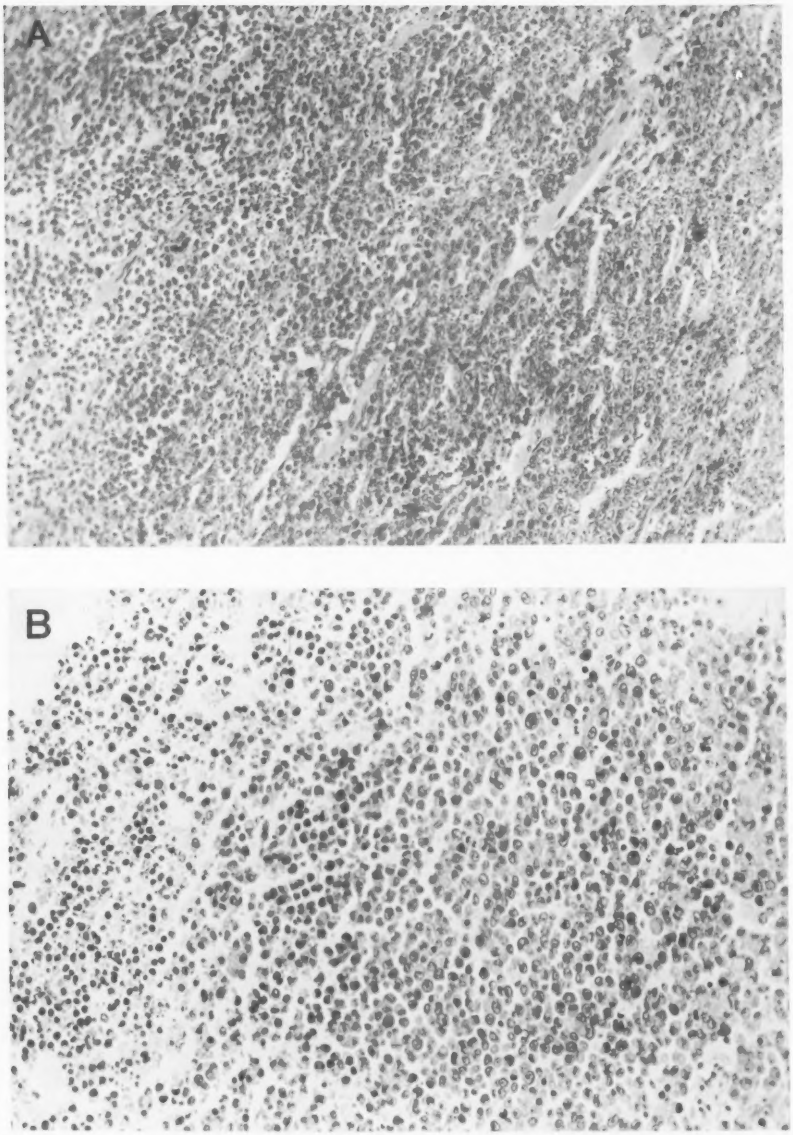

FIGURE 6.—(A): ~ 200x Walker 256/A. Cells are adhering well to each other. Striatal muscular fibers are dissociated by the tumor tissue. Necrotic elements are present in small areas (on the right). (B): 200x approx Walker 256/B. Cells are poligonal and become loose approaching the area of pyknotic and necrotic elements.

TABLE 4.—Some biological parameters concerning two lines of Walker carcinosarcoma 256

		Controls	W 256/A*	W 256/B†
Tumor mass	g		20.9 ± 1.9	20.6 ± 1.9
Food intake	g	26.9 ± 0.2	21.5 ± 1.5	7.0 ± 1.0
	mg	1500 ± 56.5	1091 ± 57.3‡	256 ± 48.0
Epididymal adipose tissue				
(mg/100 g body wt)		595 ± 21.7	463 ± 22.2	171 ± 27.4
	mg	1263 ± 22.5	1042 ± 35.8§	627 ± 33.4
Gastrocnemius muscle				
(mg/100 g body wt)		500 ± 9.4	442 ± 9.6	425 ± 14.0
	mg	259 ± 7.1	206 ± 6.1¶	142 ± 7.4
Proteins				
	mg/g	205 ± 3.6	198 ± 2.9	227 ± 2.1
Leucocytes				
x 10^3/mm^3		16.5 ± 2.0	36.8 ± 3.8	66.3 ± 10.5
Renal function**				
Urinary volume		—	D	D
Creatinine clearance		—	—	D
Blood urea		—	—	I

*14 days after tumor implant.
†9 days after tumor implant when tumor mass of both lines was 20 grams.
‡Tukey's test: c ≠ a, $P < 0.01$; c ≠ b, $P < 0.01$; a ≠ b, $P < 0.01$
§Tukey's test: c ≠ a, $P < 0.05$; c ≠ b, $P < 0.05$; a ≠ b, $P < 0.05$
¶Tukey's test: c ≠ a, $P < 0.01$; c ≠ b, $P < 0.01$; a ≠ b, $P < 0.01$
**— = no change vs controls; D = decrease; I = increase.

TABLE 5.—Compounds and treatment schedules tested on the anorexia induced by Walker carcinosarcoma 256/B in rats

Compound	Route of administration	mg/kg/dose	Daily doses*
Oxazepam	po	2-4-8-16-32	2
Aminoguanidine	po	2-4-8-16-32	2
	ip	2-4-8-16-32	2
Cyproheptadine	po	1-2-4	1
	ip	0.1-0.2-0.3-0.5-	1
		1-2-4-8-16	2
Amytriptyline	ip	1-2-4-8-16	2
Methergoline	ip	0.1-1-5	2

*Treatment schedule: from Day 2 after tumor transplantation through Day 17.

TABLE 6.—Food intake (AUC) in W 256/B-bearing rats

Days	Placebo	Cyproheptadine (dose/kg/day)				
		1 mg orally	2 mg orally	4 mg orally	100μ g ip	500 μ g ip
0-7	824.4; 59.1% (191.4)*	742.3; 48.3% (187.2)	867.9; 56.6% (192.5)	843.6; 52.1% (190.7)	857.7; 51.9% (199.3)	826.8; 53.1% (189.5)
8-11	318.6; 22.8% (175.8)	431.4; 28.0% (190.7)	460.8; 30.0% (204.2)	498.0; 30.7% (209.0)	453.9; 27.4% (202.8)	400.2; 25.7% (184.5)
12-18	252.4; 18.0% (179.2)	362.7; 23.6% (184.0)	204.6; 13.3% (185.6)	277.5; 17.1% (194.4)	340.9; 20.6% (198.4)	328.8; 21.1% (183.6)
0-18	1395.4; 100%	1536.4; 100%	1533.3; 100%	1619.1; 100%	1652.4; 100%	1555.8; 100%

*Parentheses indicate body weight in grams.

should be studied in more detail, working out the best conditions for use of this agent.

THE EFFECT OF CHEMOTHERAPY ON ANOREXIA AND CACHEXIA

Anorexia and cachexia included by tumor growth are influenced in a dual manner by chemotherapy. On one hand, the decrease of the tumor growth induced by antitumor drugs is a positive factor in reducing the tumor's influence on the host but, on the other hand, the toxicity of the antitumor agents may result in worsening of the anorexia and cachexia. As a prototype of chemotherapeutic agents effective in the treatment of Walker carcinoma 256/B growth, cyclophosphamide was given according to three treatment schedules:

(*a*) 20 mg/kg iv every other day for three times, ie on Days 5, 7 and 9 after tumor transplantation;

(*b*) 20 mg/kg/day ip for 6 times, ie on Days 5–10 after tumor transplantation;

(*c*) 120 mg/kg iv only once on Day 5 after tumor transplantation.

Table 7 summarizes the results. The efficacy of the treatment, measured by the survival time, differed, schedule (*c*) being better than (*a*) which in turn was better than (*b*). A similar pattern was seen for body weight. As regards food intake (fig 7) cyclophosphamide caused a reduction in consumption proportional to the dose given. However, after the initial drop of food intake there was a recovery to above the untreated rats. The figure shows the daily food consumption graphically, and in table 7 the area under the curve (AUC) gives a numerical index of the total amount of food eaten during the 14 days (the value is corrected for the number of surviving animals).

As expected, the decrease in adipose tissue and muscle weights was prevented by cyclophosphamide treatment to a degree that reflected the efficacy in antagonizing the drop in food intake. These findings show that chemotherapeutic agents decrease food intake in proportion to the applied single dose. However, the capacity to inhibit tumor growth is also reflected in an increase of food intake. It is likely that treatment schedules could be developed in such a way as to minimally decrease food intake at equal antitumor effectiveness.

MECHANISMS OF ANOREXIA

In searching for leads to interpret the mechanism of cancer-induced anorexia, it seems logical to refer to what is already known about the mechanisms of action of the centrally acting anorectic agents. On the basis of available data it is believed there are two major groups of agents effective in lowering food intake: the prototype drug for the first group is *d*-amphetamine; the other, most widely known drugs including diethylpropion, phentermine, and mazindol. The prototype drug for the second group is fenfluramine, other experimental compounds including quipazine, *m*-chlorophenylpiperazine, and MK-212. The anorectic action of the first group (*d*-amphetamine) requires an intact central catecholaminergic system and is related to a release of noradrenaline and dopamine. In fact, a block of catecholaminergic system (by intraventricular injection of 6-hydroxydopamine) abolishes the anorectic effect of *d*-amphetamine and its congeners (22–24). It is difficult to distinguish at the moment whether the effect of *d*-amphetamine relies more on the noradrenergic or the dopaminergic system. Schematically, it can be said that low doses of *d*-amphetamine act through the noradrenergic system (they are blocked by lesion of the noradrenergic ventral bundles) while high doses may involve the dopaminergic system too, as shown by the partial antagonism exerted by dopaminergic antagonists (eg, penfluridol).

The anorectic action of the second group (fenfluramine) requires instead an intact central serotonergic

TABLE 7.—Efficacy of cyclophosphamide given according to three schedules of treatment in rats bearing Walker carcinosarcoma 256/B

	Mean survival time		Net body weight	Tumor weight	Food intake: AUC up to		
	days	T/C x 100	(g)	(g)	Day 16	Day 25	Day 30
Controls			*	—	410	669	820
Walker 256/B	14 ± 1	—	129.6 ± 4.4	45.4 ± 3.5	196	—	—
Cyclophosphamide							
iv 20 mg/kg (3 times)	24	171	147.6 ± 5.4	55.9 ± 6.1	259	410	446
ip 20 mg/kg (6 times)	15	107	151.3 ± 7.9	37.3 ± 9.1	265	388	437
iv 120 mg/kg (once)	29†	207	177.8 ± 11.8	70.5 ± 8.2	312	498	555

*Body weight of control animals at various times can be observed in figs 3 and 5.

†5 of 10 animals were considered cured, surviving > 60 days.

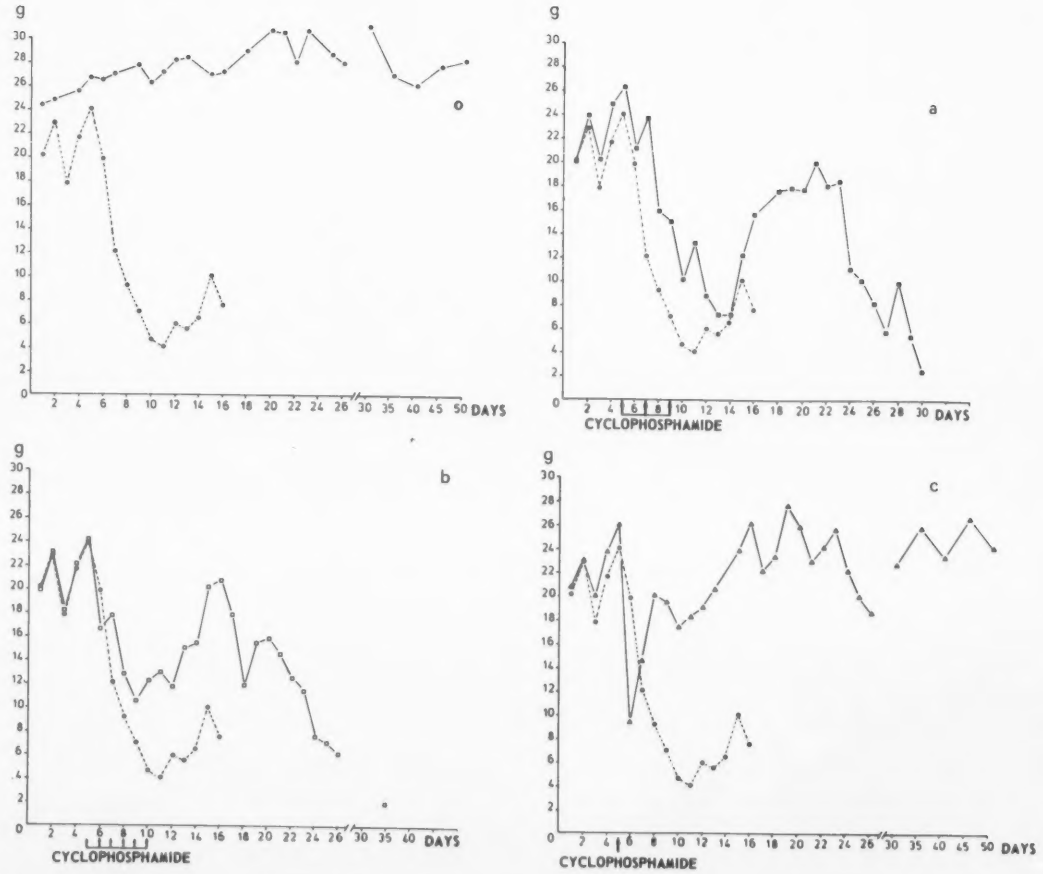

FIGURE 7.—Time-course of food consumption in W 256/B-bearing rats: ●——● normal untreated, nontransplanted rats (panel o), ●——● W 256/B-bearing rats given distilled water (panel/o/a/b/c), ■——■ W 256/B given cyclophosphamide iv 20 mg/kg 3 times (panel a), □——□ W 256/B given cyclosphosphamide ip 20 mg/kg, 6 times (panel b), ▲——▲ W 256/B given cyclophosphamide iv 120 mg/kg one single dose (panel c).

system. For the fenfluramine-like drugs, serotonin release and inhibition of the uptake of this amine (25), or direct stimulation of the serotonergic receptors (26,27), is necessary to obtain the anorectic effect. Antagonists of serotonin (such as methergoline) or lesions of the serotonergic terminals (as induced by electrolytic lesions of the midbrain raphe) completely block the anorectic effect of fenfluramine (28,29).

It should be noted that procedures or drugs that antagonize *d*-amphetamine anorexia are inactive on the fenfluramine decrease of food intake (22,30) and vice versa (28).

In relation to these findings, it was of interest to apply the approach followed to elucidate the mechanism of action of anorectic agents also to the anorexia induced by Walker carcinosarcoma 256/B. Two conditions were selected: lesion of the ventral noradrenergic bundles as a means of affecting the noradrenergic presynaptic terminals, and use of methergoline to block the serotonergic receptors.

The results obtained were essentially negative, suggesting that cancer-induced anorexia may be caused at a level different from the ones affected by anorectic agents (table 8). It should also be noted that whereas the anorexia induced by cancer growth is persistent, that elicited by anorectic agents lasts only a few days in rats, since resistance arises during repeated treatment.

TABLE 8.—Mechanisms inducing anorexia

Anorexia induced by	Effect of	
	Ventral noradrenergic bundle lesion	Methergoline treatment
d-Amphetamine	Inhibition	No effect
Fenfluramine	No effect	Inhibition
Walker 256/A	No effect	No effect

CONCLUSIONS

The growth of given experimental tumors results in an early decrease of food intake that contributes to the subsequent cachectic condition of tumor-bearing animals. This experimental situation mimics the pattern in cancer patients.

A model to study the relations between food intake, body weight, and tumor growth has been developed, using Walker carcinosarcoma 256/B transplanted sc in rats. This model also establishes the relations between the decrease of food intake and the onset of cachexia. Tumor growth results in a loss of adipose tissue and, to a lesser extent, of muscle tissue, which is not only the outcome of the decreased food intake, as indicated by experiments using pair-fed animals. Neither is the size of the tumor the major determinant in the decrease of food intake because animals bearing another line of Walker carcinosarcoma 256 (line A) do not show anorexia at an early stage of tumor growth.

These findings suggest that the anorexia induced by given tumors may depend upon a release of some principles which reduce food intake. Whatever the cause of tumor-induced anorexia, it appears that the anorexia following the growth of Walker carcinosarcoma 256/B occurs through a mechanism different from that underlying the actions of central anorectic drugs belonging to the amphetamine or fenfluramine groups.

The availability of animal models to study cancer-induced anorexia permits screening of drugs (orectic agents) that may increase food intake, and investigation of the effect on cachexia of parenteral nutrition or forced feeding with different mixtures of nutrients. Among the few drugs studied, cyproheptadine at certain doses appears to have a limited but significant effect in relieving anorexia and cachexia.

Anticancer agents, as exemplified by cyclophosphamide, counteract anorexia and cachexia by inhibiting tumor growth but they may also, at least at certain times, aggravate the decrease of food intake because of their general toxic effects. The availability of the Walker carcinosarcoma 256/B model may be useful in establishing the efficacy of antitumor agents, not only on reduction of tumor growth but also in terms of host reactions. In addition, this model could be used to study interactions between antitumoral drugs and orectic agents.

The possibility of developing drugs for counteracting anorexia and cachexia in laboratory animals may have considerable significance for the treatment of human cancers. If a drug could relieve these symptoms in patients, besides improving their quality of life, it might also enable them to maintain adequate immunological defenses and to stand up better to anticancer drug treatments or other therapies such as surgery and radiation.

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Learned Taste Aversion as a Factor in Cancer Therapy[1]

James C. Smith[2,*] and Judith T. Blumsack[2,3]

For the past 25 years numerous investigators in radiation biology and experimental psychology have been studying a phenomenon known as radiation-induced taste aversion. This phenomenon, which was first reported by Garcia and co-workers in 1955 (1), has been demonstrated with a variety of designs in laboratory animals. Essentially what happens in these experiments is that a profound aversion to a taste solution is learned by the animal after only one pairing of the taste solution with a sublethal exposure to ionizing radiation.

This report describes the phenomenon of radiation induced and other learned taste aversions and discusses the possibility that such learned aversions play some role in the dietary problems experienced by cancer patients, especially those undergoing radiation and chemotherapy.

GENERAL DESCRIPTIONS OF RADIATION-INDUCED TASTE AVERSION

A recent study from our laboratory will serve as an example of a learned taste aversion experiment. The subjects for this experiment were 128 male albino rats (Sprague-Dawley strain) with an average weight of 350 g. The rats were housed in individual wire mesh cages and kept in a constant temperature environment with a 12-hour on/off light/dark cycle. Wayne laboratory chow was available throughout the experiment.

The rats were received from the vendor and habituated to the laboratory for 3 weeks prior to the initiation of the experiment. On Day 1, the rats were deprived of water for 24 hours. On Day 2, at approximately 8 AM, they received water for 1 hour; on Day 3, they received water for 30 minutes; and on Day 4, they received water for 10 minutes. This procedure accustoms the rats to receiving their daily water ration early in the morning, and insures that they drink at this time without hesitation when the fluid is presented. At this stage the rats were randomly divided into four groups of 32 each. On Day 5, the experimental group (group 1) received saccharin followed by gamma exposure (100R whole body). The three control groups received saccharin and a sham exposure (group 2), water and a gamma exposure (group 3), or water and a sham exposure (group 4). The measure of aversion was a two-bottle (saccharin vs water) preference test for 24 hours starting the day after the gamma exposure. A summary of the experiment can be seen in figure 1.

Rats that received the saccharin-gamma pairing showed a marked aversion to the saccharin solution as compared with the three control groups. By an analysis of variance the difference between group 1 and the other groups was statistically significant, but the control groups were not different from each other.

The implication of this experiment is that pairing a normally preferred taste substance with a single sublethal exposure to ionizing radiation results in a subsequent aversion to that substance. Mere exposure to the gamma rays does not result in any long term aversion. In classical conditioning terms, the saccharin (conditioned stimulus) when paired with the irradiation (unconditioned stimulus) results in a conditioned aversion to the saccharin.

This taste aversion is a rather longlasting phenomenon. The daily 24-hour preference measures were continued for the four groups from that experiment. From the results, seen in figure 2, it is evident that with continued daily exposure to the saccharin, the aversion in the rats to the sweetened solution was extinguished in approximately 30 days.

THE CONDITIONS UNDER WHICH THESE AVERSIONS OCCUR

Numerous parametric studies have been conducted illustrating the conditions under which these radiation-induced taste aversions occur (2).

These aversions have been conditioned with a variety of taste solutions, including sucrose (3), chocolate milk (4), Kool-Aid, (5), and NaCl (6). The conditioning is more profound if the taste solution is novel to the rat (7).

Radiation-induced taste aversions have been conditioned using x-rays, gamma rays and fast neutrons, x-ray energies from 50 kv to 3 MeV, and exposure rates

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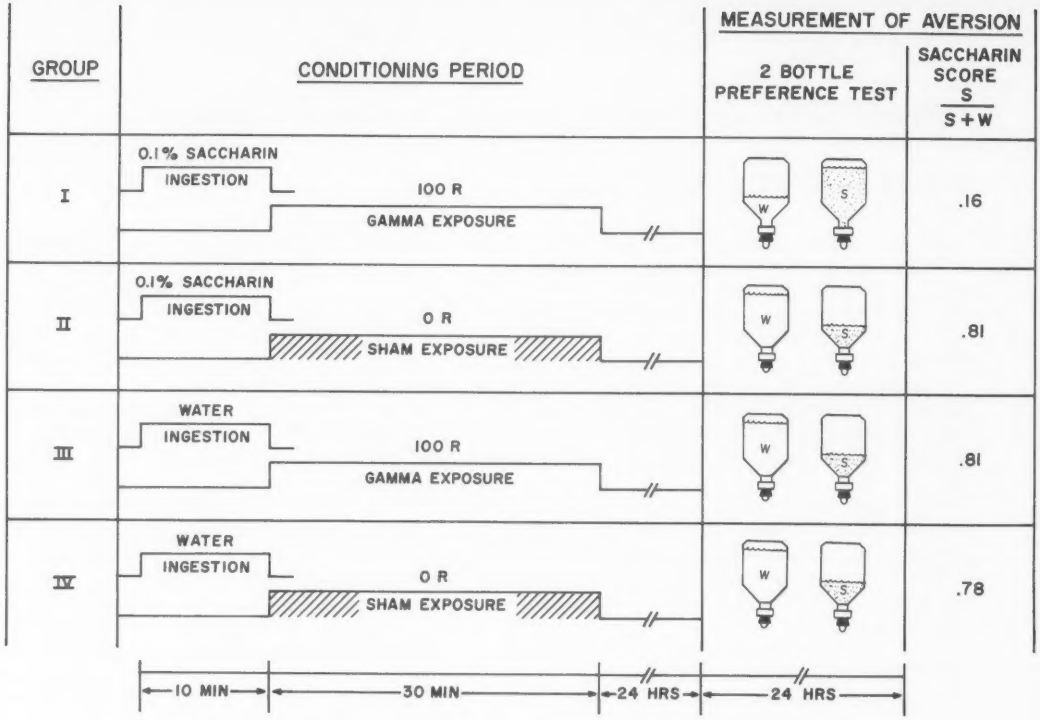

FIGURE 1.—A schematic diagram illustrates the design and results of the first experiment.

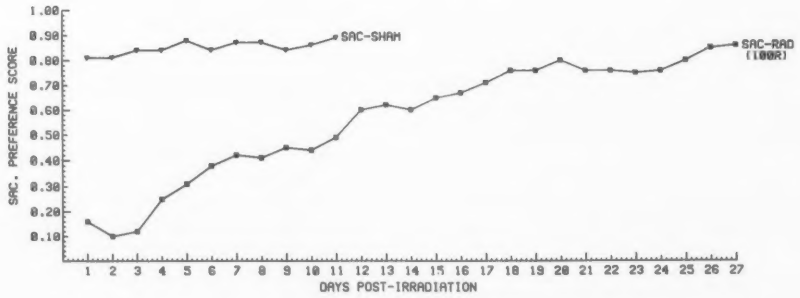

FIGURE 2.—Saccharin preference scores are plotted as a function of days following the pairing of saccharin and gamma rays. The sac-sham group received saccharin and a sham exposure on conditioning day. The sac-rad group received saccharin paired with a 100R whole body exposure.

from 0.007R/sec to 13.8R/sec (2,8). Aversions can be conditioned with exposure as low as 10R (9).

It has been shown that learned taste aversions will result from the pairing of saccharin and irradiation in a variety of temporal relationships. That is, saccharin presentation can precede or follow irradiation by several hours and yet result in aversion.

Radiation-induced taste aversion can be produced with partial body exposures (11). Exposure of the abdominal area produces more profound taste aversions than exposure of the head, thorax, or pelvis. Head, thorax, and pelvis exposures result in some learned taste aversion if the dose is as high as 250R.

A recent replication and extension of this partial body exposure work has been accomplished in our laboratory. The subjects for this experiment were 72 male Sprague-Dawley rats. The conditions for housing were identical to those described in Experiment 1 of this report, as was the procedure to accustom the rats to drinking at a specific time of the day. In the present experiment, the rats were divided into eight groups of nine animals each. The irradiation procedure differed in that the animals were placed in a Plexiglas cylindrical restraining chamber to inhibit movement and to allow a partial body exposure. On the conditioning day, the animals were given saccharin for 10 minutes and placed in the restraining chamber. Each group then was given one of the following irradiation conditions: head exposure (100R, 200R, or 300R), abdominal exposure (100R, 200R, or 300R), sham exposure, or whole body exposure (100R).

The results of the first 24-hour preference test are presented in table 1.

It is clear from table 1 that a 100R exposure results in aversion, regardless of the area exposed. Whole body exposure results in the most profound aversion, and abdominal exposure is more effective than head exposure. If one looks at the column for head exposure, little change is noticed as the dose is increased. In contrast, the strength of the aversion from abdominal exposure increased markedly as the dose was raised from 100R to 300R. This difference in the results from head and abdominal exposure is more striking if one looks at the extinction of this aversion over a 3-week period. In figure 3 it can be seen that there is little difference in the extinction curves for different doses among the head groups, but once again the effect of total dose is evident for abdominal exposure.

THE PHYSIOLOGICAL BASIS OF RADIATION INDUCED TASTE AVERSION

Throughout the history of research in radiation-induced taste aversion, the physiological basis of the aversion has been a question of great interest. Specifically, what aspect of the radiation exposure is being perceived by the organism and is serving as the aversive event? Or, in Pavlovian tems, what is the unconditioned response?

It is possible, for example, that the animal directly senses the radiation exposure, visually or by olfaction or taste, and that this sensory event is unpleasant and conditions an aversion to the taste stimulus. Two observations argue against this possibility: aversions can be produced with the head shielded from the beam (11), ruling out any essential role of vision or the other sensory inputs peculiar to the head; the rate of radiation exposure seems to be unimportant (2) making this conditioned stimulus quite unlike other sensory stimuli.

Another possible mechanism is that the aversive event involves a physiological response to the radiation. This possibility is supported by the experiments of Hunt, Carroll, and Kimeldorf (12,13), which involved unrestrained parabiont pairs of male rats united by vascular anastomosis at 26 days of age. Several weeks later they were tested to see if irradiation of one partner would produce some transferable humoral factor to the shielded partner. While one member of a pair was irradiated, its shielded partner was given saccharin to drink. Subsequently, it was noted that the shielded partner demonstrated a profound aversion to saccharin. From this and other experiments, the evidence is strong that a humoral factor is involved in the formation of the saccharin aversion. One possibility regarding the nature of this humoral factor has arisen as an outgrowth of experiments concerning the time course of the aversion. Specifically, several experiments in our laboratory led to the conclusion that the time when the animal develops the most profound aver-

TABLE 1.—Saccharin preference scores for the first 24-hour two-bottle test are presented for each exposure condition*

Gamma ray Exposure	Part of body exposed		
	Head	Abdomen	Whole body
100R	0.44	0.29	0.15
200R	0.26	0.14	—
300R	0.39	0.05	—

*The preference score for the sham exposure group was 0.88.

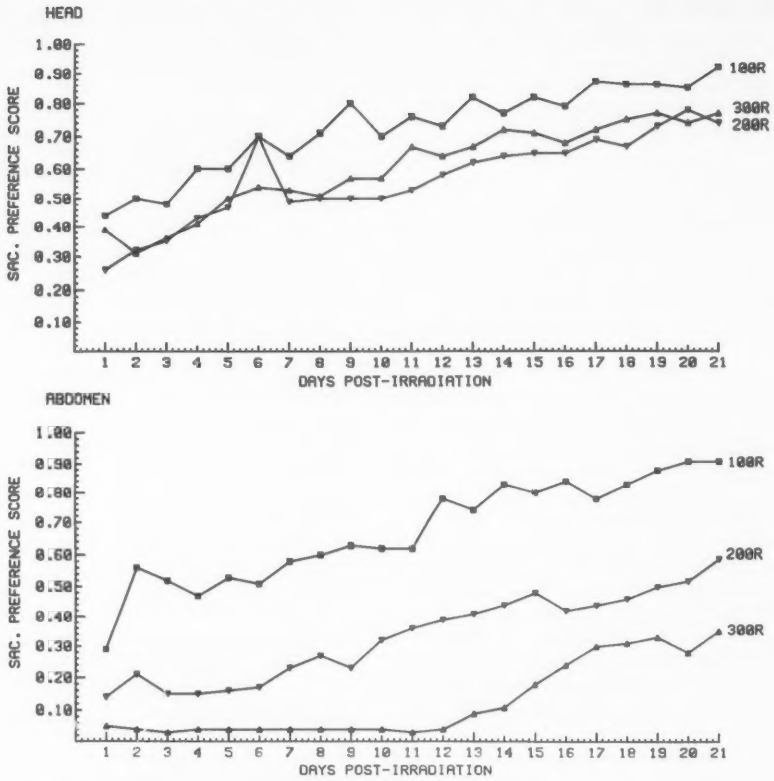

FIGURE 3.—Saccarin preference is plotted as a function of days following irradiation for groups of rats receiving head exposure (upper panel) and abdominal exposure (lower panel).

sion is when the taste solution is presented 60-120 minutes after irradiation (10,14).

After obtaining these results, we learned that other investigators have reported that the level of assayable histamine in blood is highest about 2 hours after irradiation (15). This relation between the rise in histamine and the peak aversive experience following irradiation was strong enough to justify a test of the hypothesis that antihistamine treatment of rats would inhibit the formation of radiation-induced taste aversions. It is important to note at this point that several substances (eg, atropine sulfate, sodium pentabarbital) have been tested as possible inhibitors of taste aversion learning (2). None had been found to inhibit formation of taste aversion. In marked contrast, rats injected with chlorpheniramine maleate prior to the initial pairing of saccharin and radiation failed to develop any saccharin aversion in subsequent postirradiation preference tests (16). These findings suggest that histamine plays a role in the formation of radiation-induced taste aversions, and further investigation is warranted.

It is important to recognize that radiation-induced taste aversions constitute one element of the broader category of learned taste aversions. Learned taste aversions also occur when a taste is paired with other aversive agents. For example, taste aversions can be readily conditioned by pairing a taste solution with the injection of a variety of chemical substances. More than 50 different substances have been proven to be effective in producing these profound aversions, including amphetamine, apomorphine, cyclophosphamide, ethanol, lithium, and pentobarbital.

It is highly unlikely that there is a single common factor responsible for the effectiveness of these diverse drugs (10,17) in producing taste aversions, and there is no evidence that histamine is involved in any of these conditioning experiments other than those involving ionizing radiation.

THE ROLE THAT RADIATION- OR DRUG-INDUCED TASTE AVERSIONS COULD PLAY IN CANCER PATIENTS

In considering whether learned taste aversions might have some relevance to cancer patients, it is reasonable to ask first if learned taste aversion normally occurs in man. This question was studied systematically several years ago by Garb and Stunkard (18) who surveyed subjects of varying ages regarding learned food aversions. Of the nearly 700 subjects surveyed, 38% reported at least one such learned food aversion. The existence of learned food aversions in man is further supported by considerable anecdotal evidence.

It is conceivable that learned food aversions could be of practical significance to cancer patients, in view of the fact that there are parallels between the conditions under which learned taste aversions occur and the circumstances encountered by cancer patients receiving radiation thereapy and/or chemotherapy. Specifically, cancer patients sometimes experience gastrointestinal upset associated with radiation therapy and/or chemotherapy and it is likely that these patients often ingest food in reasonably close temporal proximity to treatment. In light of these parallels, it seems worthwhile to us to try to determine if learned taste aversions occur in cancer patients. The research of Dr. Ilene Bernstein (19) addresses this question with respect to chemotherapy.

The work in our program has been specifically concerned with radiation therapy patients. Our aim has been to determine if patients receiving radiation therapy develop aversions to foods that have been temporally associated with radiation treatment. We have been using an interview technique to make this assessment.

At the outset, it is important to recognize that neoplastic disease itself affects appetite and eating behavior (20,21). Alterations in metabolism (20,22), changes in absorption (23), and anorexia (21) associated with neoplastic disease and/or with direct effects of treatment are known to occur and to affect eating behavior. Our research focuses on learned food aversions. However, our interview format must be considerably broader in scope, so that other factors affecting eating behavior and food preferences are measured. Among the components included in the interviews we are currently conducting are items consumed in the past 24 hours, estimated amounts and time consumed, other items served but not consumed, where items were consumed and who prepared them, an appetite rating, and general comments. Each day, the patients also are asked if they experienced any physical complaints, such as sore throat, difficult swallowing, nausea, vomiting, change in bowel habit, or change in taste of any foods. Weekly triceps-skin fold, midarm circumference, and weight measurements have recently been added. In addition, relevant information obtained from patient medical records is recorded separately.

The first group of patients interviewed consisted of 24 patients (10 male and 14 female) interviewed 5 days/week for 5–6 weeks. These cases included 13 treated in the pelvic region (including one patient treated in the total abdomen), four treated for disease in the lung, three treated for disease in the breast, two treated in the head and neck region, one eyelid treatment area, and one femur treatment area. The ages of the patients ranged from 39 years to 86 years with the median age in the mid-60s.

In this group of patients, we observed instances of reported decrease in appetite and/or early satiation, occasional decreased preference for meat, and reported changes in the taste of specific foods, most commonly coffee. These findings are compatible with those of other observers (24–26). Radiation-induced taste aversions, that is, aversions to foods and beverages consumed just prior to and during the course of treatment, however, were not apparent in the food preference reports and dietary patterns in these patients.

Only one of the patients in this group received upper abdominal treatment. This patient reported more difficulty with nausea and vomiting than many of the others interviewed, but there was no clear evidence of radiation-induced taste aversion to food consumed during treatment. We have recently interviewed a second patient treated in the upper abdomen. This patient reported lasting aversions to specific food associated with treatment and also reported a variety of other changes in dietary pattern and food preferences during and after treatment.

Our work is quite preliminary since we have seen thus far only two patients treated in the upper abdomen. The experience of radiation therapists and their assistants indicating that nausea, vomiting, and decreased appetite are most commonly associated with upper abdominal treatment, and the laboratory findings with animals that strong learned taste aversions are associated with treatment of the abdominal area, suggest that patients receiving abdominal treatment are those most likely to develop learned food aversions. Evaluation of this possibility, however, will require extensive further observations.

From our work it is too soon to determine if radiation-induced learned food aversions even occur in human patients and if this type of learned aversion contributes significantly to their dietary problems. We do know that a profound change in the dietary behavior of experimental animals can be produced with only one exposure to the ionizing radiation. We consider it valuable for those working in clinical practice to be aware of the experimental findings regarding

taste aversions with animals, particularly in view of the possibility of learned food aversions in other contexts, such as drug-induced aversions associated with illness itself. These latter possibilities are being investigated by Dr. Bernstein.

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Learned Food Aversions and Cancer Anorexia[1]

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SUMMARY

Evidence is presented, both from the clinic and the laboratory, that learned food aversions occur as a result of the association of foods with the discomfort induced by chemotherapy and/or tumor growth. The possible role these aversions play in the etiology of cancer anorexia are discussed and studies aimed at developing methods for preventing them are described.

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Cancer patients frequently suffer symptoms of appetite loss as a consequence of their disease and certain of their treatments (1-4). These symptoms have generally been assumed to be a direct effect of the disease or treatment and relatively little success has been encountered in efforts to alleviate these appetite problems. We have recently suggested that learned food aversions may play a heretofore unsuspected role in the development of cancer-associated anorexia (5,6).

Learned food aversions are aversions to specific foods or tastes that develop as a result of the association of those foods with unpleasant internal symptoms (ie, nausea, vomiting). In initial studies, Garcia and colleagues (7,8) reported that when animals eat a particular food before receiving a drug or radiation treatment that induces gastrointestinal (GI) discomfort they will subsequently avoid that food. This is presumably because the symptoms of the treatment are associated with the food itself. Furthermore, they avoid that specific food long after all symptoms of discomfort have subsided.

This phenomenon of learned or conditioned taste aversions has been viewed as a variant of classical conditioning with animals learning to associate a conditioned stimulus (CS) (the taste) with an unconditioned stimulus (US) (the illness) (9). This learning is evidenced by the animal's rejection of a previously acceptable and preferred food after the food has been paired with these aversive treatments.

One of the important and unusual features of food aversion learning is that it is possible to introduce a delay of many hours between the tasting of the food (CS) and subsequent discomfort (US) and still produce an aversion to the taste (8). Another important feature is that this learning occurs very rapidly. In many taste aversion experiments significant aversions are acquired in a single trial, ie, following one pairing food consumption and discomfort. Novelty of the food is also important since evidence indicates that aversions are most likely to develop to the most novel food consumed around the time discomfort is experienced (10). Repeated pairings of food and illness, on the other hand, can cause even the most familiar items to become aversive (11).

In this paper we first present evidence that children and adults with cancer acquire learned aversions to foods consumed before chemotherapy treatments that induce nausea and vomiting. Next, we describe studies using an experimental animal model to define the basis for learned food aversions and design intervention methods for preventing them. Recent evidence obtained with the model indicates that the growth of an anorexigenic tumor alone (without drug treatments) can produce learned aversions to the specific diet consumed during tumor growth. We conclude by discussing the possible implications of this evidence for a role of drug- and tumor-induced food aversions in the etiology of anorexia in patients with cancer.

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CLINICAL STUDIES

Learned Aversions to a Novel Flavor

We first investigated whether children receiving chemotherapy for the treatment of neoplastic diseases acquire aversions to foods consumed prior to drug treatments (5,6). These studies were of particular interest as learned food aversions had previously not been demonstrated in humans. Patients receiving drugs associated with a moderate to severe degree of nausea and/or vomiting (eg, cyclophosphamide, doxirubicin, cytosine arabinoside) were randomly assigned to an experimental or control group. Patients assigned to the experimental group were offered a serving of an unusually flavored ice cream shortly before their scheduled treatment. Those in the control group were not given ice cream, but were occupied for a comparable amount of time with a toy. An additional control group consisted of clinic patients who were either receiving vincristine, a drug not associated with GI discomfort, or no drug treatment. They were offered the same ice cream as the experimental group. Patients were tested for the development of aversions 2–4 weeks later by being offered a choice between eating that ice cream or playing with a game. The results showed that patients in the control groups were three times as likely to choose the ice cream than patients in the experimental group ($P < 0.01$). Thus children will avoid eating a food that has previously been associated with GI-toxic chemotherapy. This aversion is not caused by the GI-toxic drugs alone, since patients that had received these drugs but were not exposed to the ice cream flavor were not averse to eating the ice cream. That the ice cream was not distasteful is indicated by the acceptance of it by patients who had previously tasted it at a time when they were not receiving GI-toxic therapy. Therefore, these results demonstrate that children acquire aversions to a novel flavor when it is consumed before treatment that induces GI discomfort.

We next examined medical oncology patients to determine whether adults, like children, would develop learned taste aversions. Adult patients presumably have a more complete understanding than children that their discomfort is due to their therapy. Additionally, fewer foods are novel to adults. Consequently, adults might be unlikely to form significant taste aversions in a single session. Since adult cancer patients form a much larger proportion of the clinical population than children, careful evaluation of such patients would be important for accurately gauging the extent to which learned food aversions may be expected to affect cancer patient populations.

Seventy outpatients (male and female, age 17–77 years) receiving intravenous (iv) doses of chemotherapeutic drugs were included. Subjects were divided into three groups based on their scheduled clinic treatments: one group was receiving 5-FU; a second group was receiving other GI-toxic drugs (eg, cyclophosphamide, adriamycin, nitrogen mustard); and a third group was a control group receiving either no drug treatment or iv vincristine. Subjects in all groups were pre-exposed to one of two distinctively flavored ice creams 15 to 60 minutes prior to an examination with or without a drug treatment. In each group, subjects were randomly assigned to receive 53 g of either Maple Nut (MN) or Hawaiian Delight (HD) (orange-pineapple) ice cream. Testing occurred at a later clinic visit (mean: 5 weeks later). All subjects were tested for their flavor preference by being offered two cups of ice cream (MN and HD). Subjects were asked to taste both flavors, indicate which they preferred, and eat as much of each as they wished. Flavor preference and amount consumed were recorded. Preference scores, based on ice cream consumption during testing, are presented in table 1. Subjects in the experimental groups (5-FU and GI-toxic) who consumed MN during conditioning had a lower preference for MN ice cream than those who consumed HD. This effect was not seen in the control group where specific flavor pre-exposure had no effect on preference. Statements by subjects concerning their flavor preference were consistent with the consumption measures; a significantly lower percentage of experimental subjects preferred the flavor they had consumed before their treatments than control patients.

These results indicate that in adults (as in children) the consumption of a distinctively flavored ice cream before GI-toxic chemotherapy is associated with a significantly lower preference for that particular flavor during subsequent testing. Apparently the cognitive development of adults, which enables them to understand that their discomfort is due to their therapy rather than an ice cream flavor, does not override this conditioning. These results are particularly striking because the subjects in this study reported relatively mild discomfort as a consequence of their treatment. Eighty percent of experimental group patients reported experiencing mild nausea, or no nausea at all. It is therefore possible that patients receiving treatments that produce more severe symptoms would experience greater aversions.

TABLE 1.—Preference for maple nut (MN) ice cream (g consumed/total g ice cream consumed)

	Flavor pre-exposure	
Treatment group	Maple nut (MN)	Hawaiian delight (HD)
5-FU	0.38	0.51
GI-toxic	0.38	0.54
Control	0.40	0.41

$P < 0.05$, ANOVA

LEARNED AVERSIONS TO DIET ITEMS

We have recently been evaluating whether patients form aversions to familiar and/or preferred foods in their usual diets, and not just novel foods. To accomplish this we have requested pediatric patients (or their parents) to complete diet inventory forms by listing: (*a*) favorite foods; (*b*) foods they are reluctant to eat; (*c*) two typical breakfast, lunch, and dinner menus; and (*d*) any specific foods they have eaten in the past 4–5 hours. For patients in the experimental group who are about to receive a GI-toxic chemotherapy treatment, the specific items consumed 4–5 hours prior to therapy were considered potential candidates for the formation of an aversion. Two to 4 weeks later at a subsequent clinic visit, patients were requested to fill out another inventory, much like the first, requesting items (*a*), (*b*), and (*c*) above.

Thus far two inventory forms of food preference for 58 patients have been compared to see if there were systematic changes in the way patients rate the specific food they ate just before their therapy. An aversion was scored when a specific food eaten before GI-toxic drug treatments was no longer preferred, actively disliked, or no longer listed in usual menus. The number of patients showing at least one aversion was then determined. The control group consisted of patients receiving vincristine or no drug. The results (table 2) revealed that nearly half the patients receiving chemotherapy associated with GI discomfort showed aversions. This was compared to only 12% of patients in the control group who experienced no nausea and vomiting. The difference between these two proportions is significant ($P < 0.01$). Excluding specific aversions, inventories from patients receiving GI-toxic chemotherapy did not undergo more changes from session 1 to session 2 than controls. We therefore suspect that the changes we have noted are fairly specific to foods eaten before GI-toxic therapy. Thus learned food aversions may occur not only to a novel food presented by the experimenter just before drug administration, but also to foods in the patient's usual diet that happen to be eaten up to several hours before treatment.

These studies were confined to chemotherapy treatments given in a single clinic visit. However, these patients actually receive many such treatments. If half or even a quarter of them are associated with the formation of aversions, we may be looking at a significant etiologic factor in the frequent reports of capricious and frustrating changes in food preferences experienced by these patients. It is also possible that these learned food aversions are significant in the development of anorexia and weight loss seen in patients with cancer. Importantly, if a learning mechanism does account for at least part of the observed appetite loss, intervention approaches that alter the stimulus associations may prove successful in alleviating these symptoms.

TABLE 2.—Aversions to foods

	Number of patients showing aversions
Patients receiving GI-toxic chemotherapy	16/33 (48%)
Patients receiving vincristine or no drug	3/25 (12%)

$P < 0.01$

EXPERIMENTAL ANIMAL MODEL

In order to more thoroughly define conditions leading to learned food aversions and to evaluate intervention procedures to prevent their occurrence, we have initiated studies using an experimental animal model. In the initial studies we used a conditioned taste aversion paradigm and found that a single injection of chemotherapeutic drugs (eg, cyclophosphamide, adriamycin) in dosages comparable to those used clinically, could produce aversions to a saccharin solution in rats (12). We next designed a paradigm that would more closely model conditions in the clinic. This learned food aversion model involved exposing rats to a sequence of cyclophosphamide injections (20 mg/kg) and evaluating whether they developed aversions to the food (a complete rat diet, AIN meal), which was continuously available during drug treatments. Aversions to the AIN meal were assessed in a 24-hour preference test with AIN and a novel diet available. Results of studies using this model express AIN preference as the ratio of AIN consumption to total food consumption. Reduced intake of AIN relative to the choice diet is reflected in low ratios. We found significant reductions in preference for AIN diet (drug treated group: preference ratio of 0.16, versus saline treated controls: preference ratio of 0.58) indicating that a series of chemotherapy injections can produce a reliable aversion to the food which was continuously available during those treatments.

Intervention Approaches

In these studies we used the food aversion model to test a variety of intervention methods for reducing or eliminating learned food aversions. The basic study was repeated, with the inclusion of additional groups which received an intervention manipulation as well as a sequence of drug treatments. The success of these intervention methods was evaluated by determining the degree to which they blocked or reduced aversions to the AIN diet. Approaches that have been evaluated include: (*a*) withholding all food for 6 hours before and after each treatment; (*b*) introducing a novel flavor in

the water around the time of each treatment; and (c) replacing the standard AIN diet with a novel food on treatment days. Food deprivation and novel liquid interference stimuli did not reduce the magnitude of aversions to the AIN diet. The only method that significantly reduced the magnitude of the drug-induced food aversions was the introduction of a novel diet on treatment days. We are continuing these studies in an effort to identify the parameters determining the effectiveness of intervention approaches so that successful approaches may be modified and implemented in the clinic.

Tumor-induced Aversions

The preceding clinical and laboratory studies have pointed to the role of learned food aversions in contributing to the appetite loss experienced by patients receiving treatments with severe and unpleasant side effects (ie, chemotherapy, radiotherapy). Although anorexia induced by antitumor therapy is an important problem, it has long been known that tumor growth alone can produce severe anorexia (13,14). We suspected that learned food aversions might be of more general significance if learned aversions develop in response to the association of a diet with aversive physiological effects of the tumor itself. Thus, tumor-induced appetite loss, like drug-induced appetite loss, could be based indirectly on learned aversions with chronic unpleasant symptoms secondary to the tumor acting as the unconditioned stimulus, rather than the acute effects of a drug injection.

We investigated this hypothesis in rats bearing transplantable tumors that produce anorexia and weight loss. A polyoma virus-induced sarcoma (PW-739) was subcutaneously implanted in a group of experimental animals. Tumor-bearing and control animals were given continuous access to AIN diet for 10 days in the middle to late stages of tumor growth. Aversions were assessed in a preference test like those in the previously described food aversion studies.

During the 10 day diet exposure period, intake of AIN diet by tumor-bearing rats declined to levels considerably lower than controls. Mean intake on the last 2 days of this period was 9.9 g for tumor-bearing rats, compared to 15.7 g for controls ($t_{14} = 2.54$; $P < 0.05$) (table 3). Mean AIN preference scores are presented in table 4; they indicate that tumor-bearing animals appear to have developed a pronounced aversion to the AIN diet that had been available during recent tumor growth. In addition, striking elevations of 24-hour food consumption were seen in tumor-bearing animals but not controls when an alternate diet was available. Food intake of tumor-bearing animals (table 3) showed an 85% increase over pretest intake levels. Thus tumor-bearing animals, which had been consuming considerably less AIN diet than controls, ate as much or more than controls when a novel diet was introduced.

TABLE 3.—24-Hour food intake

	Tumor	Control
Average pretest food intake	9.9 g	15.7 g
Average preference test food intake	18.3 g	17.4 g
% Increase in food intake	85%	11%

These results suggest that tumor-bearing animals associate their tumor-induced discomfort with their diet and that these aversions contribute to tumor-induced anorexia. However, we need to consider whether the decreased AIN preference manifested by tumor-bearing animals was not due to a learned association but was a direct effect of tumor growth on taste preferences or responsiveness. DeWys (15) has reported that tumor growth alters taste responsiveness of cancer patients as well as laboratory animals. To determine whether these AIN aversions were due to general tumor effects or specific associations we ran another study using a crossover design and two different pre-exposure diets. Five weeks after tumor implant, groups of tumor-bearing and control animals were assigned to one of two diets (AIN or NIH-07), they received continuous access to one of these diets for 21 days. On Day 22 they received a preference test with a choice between these two diets for 24 hours. Preference for the pre-exposed food was calculated by dividing consumption of the pre-exposed food by total food consumption. Tumor-bearing animals showed a significantly lower preference for the pre-exposed food (or the food paired with tumor growth) than controls (table 4). These results support the idea that aversions are specific to the diet the animals were exposed to during tumor growth and represent a learned association. This is emphasized by examining AIN preference of tumor-bearing animals. Preference was quite different depending on pre-exposure experience: ie, 0.17 for AIN diet if animals were pre-exposed to AIN and 0.88 for AIN diet if they were pre-exposed to NIH-07. Obvi-

TABLE 4.—Preference for AIN diet in 24-hour choice test

Groups	AIN consumed (g)/ total food consumption (g) (± SEM)
Tumor	0.11 (± 0.05)
Control	0.48 (± 0.1)

$P < 0.01$, t-test

ously tumor growth alone is not a sufficient condition for the development of an aversion to AIN diet.

These studies indicated that learned food aversions occur in animals that are anorexic as a consequence of tumor growth, and they further demonstrated that it was possible to increase food intake of these animals by presenting a new diet. These results suggest that learned food aversions play a causal role in the development of tumor anorexia.

CONCLUSIONS

In summary, these studies have indicated that learned food aversions arise in humans and animals as a result both of therapy treatments, and, at least in animals, as a result of tumor growth itself. Food aversion learning has evolved in rats and many other species enabling them to learn to select needed nutrients and avoid toxins (7,16). This mechanism is clearly adaptive in that it allows organisms to associate the delayed internal effects of toxins and imbalanced nutrients with the taste of consumed foods and to adjust their intake accordingly. However, this mechanism may be triggered under inappropriate circumstances, as in the case of patients receiving cancer treatment or tumor-bearing animals, who associate the discomfort and illness induced drugs or tumor with specific foods. It appears likely that this mechanism plays a role in the anorexia produced by certain tumors and in the aversions and appetite loss seen with certain antitumor therapies. An understanding of the factors controlling the acquisition of these aversions may enable us to assess the degree to which they contribute to cancer anorexia and to propose methods for preventing them.

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Clinical Parameters Related to Anorexia[1]

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SUMMARY

Caloric intake was studied in 89 cancer patients who recorded diet diaries. Twenty-five percent had caloric intake below their calculated basal energy expenditure (BEE). An additional 45% had caloric intakes between 1.0 and 1.5 x BEE. Patients reported symptoms referable to the oronasal area and the gastrointestinal tract as possible factors in decreased eating. Food intake is controlled by several categories of cues and one or more of these may be altered in cancer patients to decrease caloric intake.

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Reduced caloric intake as a systemic effect of cancer has been studied in animal models for many years but has been less thoroughly studied in humans. The relative importance of reduced caloric intake versus increased caloric consumption in the weight loss of cancer patients has been debated. Recent studies suggest that both decreased intake and increased consumption are important determinants of negative caloric balance in cancer patients (1).

We present a preliminary report of results from a multi-institutional study evaluating anorexia in cancer patients. These results support the conclusion that decreased caloric intake is important in the weight loss of cancer patients. Symptoms reported by patients provide clues to pathophysiologic mechanisms of decreased caloric intake.

MATERIALS AND METHODS

Patients with cancer of different sites and stages were enrolled in a multifaceted protocol at three participating institutions. Variables concerning patient status at the time of entry into the study were recorded and entered into a centralized computer file. Caloric intake was estimated from 3-day diet diaries using a computerized nutrient analysis system.[5] Symptoms that might be related to food intake were elicited by a semi-structured interview.

Basal energy expenditure (BEE) was calculated for each patient as follows. Ideal weight for height and sex was determined from standard tables (2). Then using either ideal weight or real weight, whichever was smaller, and height, we calculated body surface area (BSA) from the equation (3):

$$BSA = 0.007184\ W^{0.425}\ H^{0.725}.$$

Daily BEE was then calculated using the coefficient K_{SA} based on age and sex (4) using the equation:

$$BEE = 24\ K_{SA}\ BSA.$$

This approach gives values comparable to that of the Boothby and Berkson nomogram (5) and has the advantage of being performed by a computer.

RESULTS

The average daily caloric intake (from three-day diaries) at entry to this study for 89 patients is shown in figure 1. Caloric intakes ranged from 543 to 3905 and the median intake was 1831 calories. An analysis correlating rate of weight loss and caloric intake is in progress.

The caloric intake data are displayed in relation to calculated BEE in figure 2. For reference, we have drawn lines on this figure for caloric intake identical to BEE and for caloric intake 50% above BEE. A moderate level of activity requires a caloric intake about 50% above BEE.

Twenty-two patients (25%) had caloric intakes below their calculated energy expenditure. In 40 patients (45%) energy intake was between basal expenditure and 50% above BEE. In 27 patients (30%) caloric intake was more than 50% above BEE.

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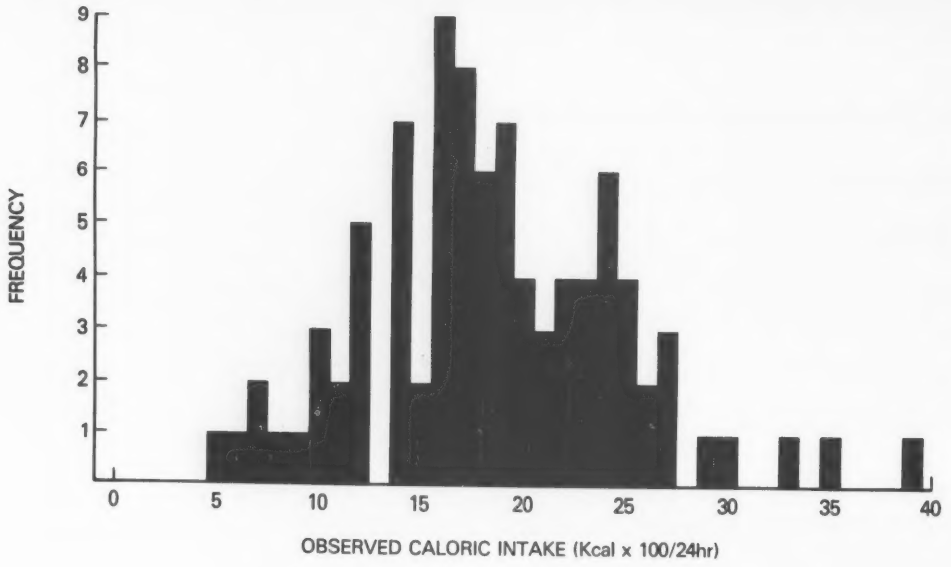

FIGURE 1.—Average daily caloric intake for 89 cancer patients.

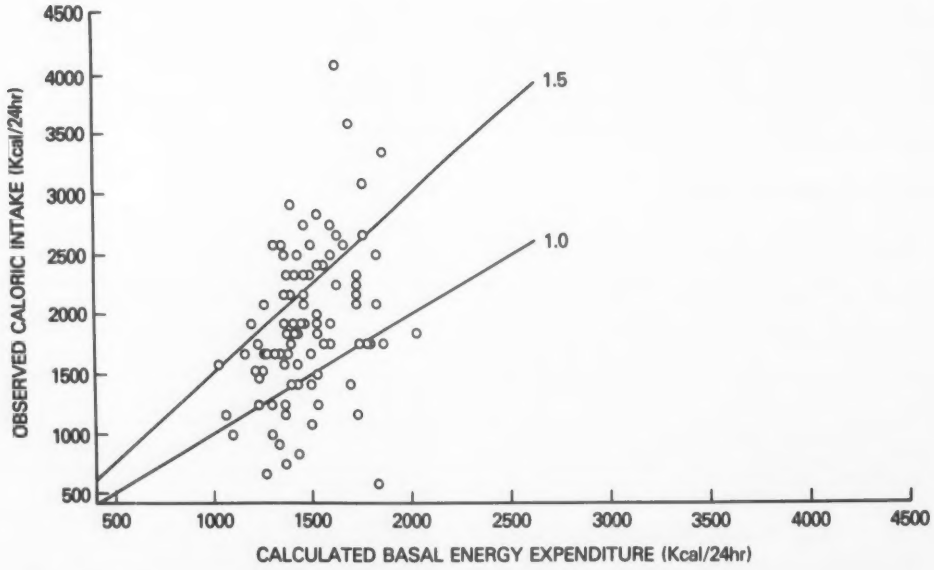

FIGURE 2.—Correlation between observed caloric intake and calculated basal energy expenditure. The line labeled 1.0 is the line of identity of caloric intake and basal energy expenditure and the line 1.5 represents caloric intake 50% above basal expenditure.

In an interview, patients were requested to report any symptoms that might be interfering with eating. One hundred and sixty-nine patients completed this interview, including 82 who were included in the caloric intake analysis presented above. Eighty-four patients reported one or more symptoms listed in table 1. Symptoms referable to the oronasal area were most frequent and were reported in one form or another by 67 patients. Thirty-five patients related symptoms referable to the gastrointestinal tract with the most frequent being a sense of filling up quickly (22 patients). Several patients reported decreased eating as a side effect of therapy. Among 93 patients who had received chemotherapy, 15 reported that side effects from chemotherapy interfered with eating. Seventy-one patients had received radiation therapy, but only three related this to eating problems.

TABLE 1.—Symptoms that might interfere with eating

Symptom	No. of patients reporting this symptom
Altered smell	21
Smell loss	10
Altered taste	53
Taste loss	17
Chewing problem	13
Soreness in mouth	7
Dryness in mouth	14
Swallowing problem	15
Nausea	9
Vomiting	4
GI obstruction	5
Fill up quickly	22
Constipation	6
Diarrhea	4
Pain	14
Infection	1
Don't feel like eating	29
Side effects of chemotherapy	15
Side effects of radiation	3
Psychosocial	7
Socioeconomic	1
Metabolic	6
Others	8

DISCUSSION

The role of insufficient caloric intake in the pathophysiology of cachexia has been referred to by previous speakers and will be discussed throughout this symposium. The present study reports the range of caloric intakes observed in a population of cancer patients and documents profound hypophagia in many of these patients. Since caloric requirements vary with height, weight, age, sex, and activity level, we have attempted to relate these observed caloric intakes to calculated energy expenditure. This comparison leads to the conclusion that a majority of patients studied do not take in enough calories to maintain a moderate activity level. It is tempting to postulate that the decreased activity level observed in cancer patients may be related to inadequate caloric intake and this is currently being analyzed.

The reduced caloric intake observed in this study contrasts with the nearly normal caloric intake reported in a small series of lung cancer patients who were losing weight (6). Perhaps the differences are due to differences in stage and site of disease. Alternatively, in some patients weight loss may be related to increased energy expenditure rather than decreased caloric intake. Measurement of energy expenditure using whole body calorimetry would resolve the relative role of decreased eating versus increased energy expenditure in the weight loss of cancer patients.

As has been discussed previously (7,8), food intake is controlled by an integrated system in which multiple cues impact independently on food intake control. This integrated system may be viewed as having four major components: a central integrating and ingestion controlling center; a system of sensors in the oronasal region; a system of sensors (primarily volumetric) in the upper gastrointestinal system; and a system of sensors that are responsive to changes in metabolites and hormones in the blood.

In considering how food intake control may be altered in the cancer patient, it is worthwhile to make the distinction between aberrations of the control system and aberrations of the parameter being sensed by the control system. Regarding the central integrating and ingestion controlling system, Morrison (8) has reviewed the evidence for normal function of this system in cancer-bearing animals while Fisher (9) has presented evidence that one of the parameters sensed by this central system may be altered in the tumor-bearing animal.

The system of sensors in the oronasal region normally provides strong positive stimulation of food intake. Abnormalities of taste sensation have been reported in several studies in cancer patients (10,11). These abnormalities have been correlated with reduced caloric intake in previous studies (11,12) but in our unpublished analyses currently in progress, the correlation is less clearcut, perhaps because of the multiplicity of cues impacting on the food-intake control center.

Symptoms referable to the gastrointestinal tract point to the possible role of gastrointestinal volume receptors in reduced food intake. The blunting and reversal of response to caloric dilution with nonnutritive bulk in tumor-bearing rats reported by Morrison (13,14) also points to the role of volume receptors in reduced caloric intake in the cancer host. One of us has previously postulated that altered taste sensation may decrease the production of digestive secretions, which could delay digestion and thus cause more

prolonged stimulation of volume receptors (7). Also, atrophic changes in the small intestine in cancer patients (15) may delay digestion and assimilation of nutrients. These atrophic changes are not specific to malignancy. DNA loss-rate studies indicated that these atrophic changes are due to decreased production of mucosal cells rather than increased turnover. Protein malnutrition and starvation are known causes of decreased mucosal cell production. Barry concluded that these epithelial changes were the result of a patient's weight loss and not a cause of it (15). In the present formulation, these atrophic changes, once they have developed, may contribute to perpetuation of weight loss. In addition, there may be wasting of the muscle of the stomach wall paralleling wasting of skeletal muscle[6] further contributing to delayed gastric emptying and prolonged stimulation of volume receptors.

Vague symptoms such as "don't feel like eating" might reflect alterations in the systems monitoring blood metabolites and hormones. Focusing our discussion on one of these—the glucose-insulin sensing system—Morrison (8) has presented evidence on the preservation of the normal response to exogenous insulin. However, endogenous insulin production may be slightly blunted in patients with advanced cancer (16). Thus in this instance the control system may be intact, but the parameter being sensed by the control system may be altered. Also, altered carbohydrate metabolism in cancer patients (17) includes increased glucose production (from lactate, alanine, and other gluconeogenic precursors) and this increased glucose production could be sensed by the glucose-insulin sensing system to result in lower caloric intake.

In conclusion, reduced caloric intake is an important determinant of cachexia in the cancer patient. It is likely that multiple aberrations in the food-intake control system contribute to reduced food intake. Future research should identify the relative role of each aberration in individual cancer patients.

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Summary of Discussions on the Anorexia Session of the Conference on Nutrition of the Cancer Patient

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After the presentations on anorexia, several topics were discussed which are paraphrased and condensed in the following paragraphs.

In response to questions, the mechanism of elevation of free plasma tryptophan was discussed further by Dr. Fisher. His patients had elevated free fatty acids which could displace tryptophan from binding to albumin. In addition, the patients had mildly depressed serum albumin concentrations. Dr. Fisher also noted that competition between plasma tryptophan and competing neutral amino acids may influence brain tryptophan levels. Dr. Garattini asked whether there was increased serotonin synthesis in the brain or decreased serotonin receptors. Dr. Fisher replied that he had evidence for increased brain 5-hydroxyindolacetic acid as an indirect measure of serotonin synthesis.

Dr. Schersten asked whether Dr. Fisher had attempted to inhibit lipolysis with insulin as a method to reduce free fatty acids which might then reduce the plasma free tryptophan. Dr. Fisher has not studied this approach, but he noted that insulin has a profound effect on brain serotonin concentration. Dr. Schersten also asked about other effects of serotonin, such as insomnia and encephalopathy. Dr. Fisher commented that abnormalities of multiple amino acids are probably involved in encephalopathy. Encephalopathy (hepatic) is being treated with branched-chain amino acids by Dr. Fisher, and he has noted improved appetites in patients so treated. Dr. Morrison pointed out the complexity of function of the whole animal and urged caution in ascribing changes in eating to changes in tryptophan or serotonin. He noted that, in an animal tumor model, feeding tryptophan in excess may actually increase food intake.

The panel was asked what was the best animal model for the study of anorexia. Dr. Garattini noted that the rapidly growing tumor model he presented is useful for measuring an early type of anorexia. Dr. Morrison pointed out that in rapidly growing tumors, depression of motor activity is more prominent and interferes with eating behavior. He said that slower-growing tumors may permit a purer study of control of food intake with less involvement of motor activity.

Dr. Morrison was asked which came first, alteration in motor activity or reduction in food intake. He replied that the reduction in food intake occurs in all the tumors that he has examined. It starts either at the same time as or before the reduction in motor activity. In the Morris 5123 hepatoma, there is reduction in food intake progressively throughout about three quarters of the life of the tumor. There is at no point any reduction in motor activity in that particular model.

Discussion regarding the hypothesis of tumor-related learned food aversion, presented by Dr. Bernstein, included a question about the duration of acceptance of the new diet to which the animals were crossed-over. Dr. Bernstein reported that she hadn't followed intake of the new diet for more than 24 hours but anticipated that the animals would quickly form aversions to each food that was associated with tumor-related ill effects.

Regarding treatment-related learned aversions, both Dr. Bernstein and Dr. Smith pointed out that intervals between eating and therapy as long as 8 to 12 hours may still be associated with the development of learned aversions.

This series of presentations and the spirited discussion that followed indicate that these issues are under intensive study in many laboratories and clinics. These studies in progress and additional ones stimulated by this conference can be expected to improve our understanding of anorexia in cancer.

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Carbohydrate Metabolism in Cancer Cachexia[1]

C. P. Holroyde,* and G. A. Reichard[2]

SUMMARY

A profound loss of body mass and energy reserves is a characteristic feature of cancer cachexia. Because glucose is a major energy-yielding fuel, abnormalities of carbohydrate metabolism may prove to be important in the development or end-result of this common syndrome. In this paper, we review the known alterations of glucose and lactate metabolism that occur in patients with malignant tumors.

[Cancer Treat Rep 65 (Suppl 5):55–59, 1981]

Cachexia is usually defined as a profound constitutional disorder in which debility and malnutrition are associated with the presence of chronic disease. The association of cachexia with human malignancy is both common and well-recognized. Although, in general, the presence of cachexia denotes a poor prognosis, surprisingly little information ia avialable in the medical literature regarding the metabolic consequences of this syndrome. At least in part, the paucity of data may be due to the heterogeneous nature of the cancer patient population in which the syndrome of cachexia may be metabolically nonspecific. In this paper, we attempt to summarize the known abnormalities of carbohydrate metabolism occurring in cachexia, with particular reference to the metabolism of glucose and lactic acid.

Although a subject of current speculation and interest, reports that carbohydrate intolerance occurs with increased frequency in cancer patients have appeared in the medical literature over the past several decades (1–4). Glucose intolerance is evidenced by heightened concentrations and delayed clearance of blood glucose following oral or iv glucose administration and may, in part, be due to tissue insensitivity to insulin as well as a blunted β-cell insulin secretory responsiveness to hyperglycemia. In this regard, cancer patients are known to have a decreased sensitivity to the hypoglycemic action of exogenous insulin (4,5) and, when challenged with a glucose load, respond with smaller than anticipated increments in blood insulin concentrations relative to the prevailing hyperglycemia (4). It should be noted that carbohydrate intolerance as defined occurs in the presence of normal fasting blood glucose concentrations and that no clear relationship exists between human cancer and diabetes mellitus.

In the context of cancer cachexia, it is pertinent that numerous clinical and metabolic events are known to be associated with impaired glucose tolerance. Included among these are starvation (6,7), bed rest (8,9), composition of the antecedent diet (10), sepsis (11), and malnutrition (12). Although insulin binding to receptors is reported to be normal in cancer patients (4), some of these factors are capable of altering tissue sensitivity to insulin as well as insulin secretory mechanisms. With rare exceptions (5), abnormal glucose tolerance in cancer patients is associated with the presence of at least one of the above factors, making it difficult to establish the primacy of cancer as the cause of the intolerance.

Additional evidence for altered glucose metabolism in cancer patients came from studies of endogenous glucose production and utilization using isotope tracer techniques. In earlier reports, little difference in the rates of glucose production and oxidation were observed in patients with cancer (13,14), although some displayed moderately elevated rates of glucose recycling (13). This cyclic metabolic pathway, in which glucose is converted to lactic acid by glycolysis and then reconverted to glucose in the liver, is referred to as the Cori cycle. Utilization of lactic acid by peripheral tissues would normally provide the tumor-bearing patient with maximum energy available from glucose oxidation. Although controversial (15), gluconeogenesis from lactate is an energy-requiring process that may play a role in excessive energy expenditure of the host (16,17).

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Recently, when cancer patients with and without progressive weight loss were compared, major differences in rates of glucose production and Cori cycle activity were noted (16). As shown in table 1, cancer patients with stable body weight had rates of total glucose turnover and Cori cycle activity similar to that observed in normal, overnight-fasted subjects. In contrast, patients with progressive weight loss displayed marked increases in total glucose turnover and Cori cycle activity with the greatest values being obtained in patients with increased BMR. Under steady state conditions, total glucose turnover is equal to the rate of glucose production and utilization. Therefore, increased rates of glucose production and utilization in patients with progressive weight loss are entirely accounted for by enhanced Cori cycle activity. This is shown by the similarity in values for the difference between total glucose turnover minus Cori cycle activity. Although these studies show that altered glucose metabolism is associated with malignant cachexia, it is not possible to definitely implicate the tumor as the direct causal factor. It should be noted, however, that progressive weight loss induced by total starvation in normal subjects results in decreased total glucose turnover (table 1). These results are clearly different from the majority of cancer patients with progressive weight loss in whom even a normal caloric expenditure and glucose turnover rate seem inappropriately elevated.

In addition to carbohydrate intolerance and heightened rates of glucose turnover and Cori cycle activity, hypoglycemia, a syndrome of diverse etiology, has also been reported as a rare complication in patients with certain extrapancreatic tumors (18–21). Despite the propensity for malignant tumors to secrete biologically active peptides, the extrapancreatic production of insulin or insulin-like material surprisingly does not appear to occur. Because glucose turnover rates are markedly elevated in this syndrome, the most frequently cited cause of tumor-associated hypoglycemia is an excessive consumption of glucose. It should be noted that these tumors are invariably of great size (18) and generally of mesenchymal origin. In the normal human, hypoglycemia provokes an increase in endogenous glucose production to restore blood glucose concentrations to normal. In hypoglycemic cancer patients, however, evidence suggests that this does not occur (18). To maintain blood glucose concentrations in such patients, massive quantities of glucose must be administered (18). Thus inadequate caloric intake may be an important contributing factor under these uncommon circumstances.

The observation that total glucose turnover and Cori cycle activity may be strikingly elevated in some cancer patients in whom blood glucose and lactate levels are essentially normal shows indirectly that tumor glycolysis may lead to increased lactate production and that host-tumor competition for glucose may significantly affect overall fuel economy. With the exception of isolated case reports in patients with hypoglycemia who were receiving exogenous glucose infusions (19,21), lactate production has not been directly measured, to our knowledge, in a homogeneous group of cancer patients with a common solid tumor.

To evaluate the possible effect of tumor glycolysison whole-body lactate metabolism, we recently studied 20 patients with metastatic colorectal cancer using an isotope-tracer technique (22). As shown in figure 1, increased rates of lactate production were observed when values were compared with control subjects of comparable age and sex. The cancer patients were characterized by a moderately increased rate of lactate oxidation, and a twofold increase in nonoxidative lactate disposal. At least in part, conversion of lactate to glucose may account for the greater difference observed in nonoxidative disposal in cancer patients in whom the percent glucose derived from lactate was found to be significantly increased (22). For both control subjects and cancer patients, there was a direct correlation between venous plasma lactate concentrations and lactate production rates, although unfortunately, the overlap in values detracts from the clinical usefulness of this observation. There was also a direct correlation between lactate production rates and the percent CO_2 derived from plasma lactate, the rates of lactate oxidation, the rates of nonoxidative lactate

TABLE 1.—Glucose metabolism in cancer patients and normal subjects

	Total glucose turnover (TGT)	Cori cycle (CC)	TGT−CC
	gm/1.73m²/24 hr		
Normal, overnight fast	200	36	164
Normal, 7-day fast	144	36	108
Cancer, stable weight	187	33	154
Cancer, progressive weight loss	268	115	153
Cancer, progressive weight loss with increased BMR	370	212	158

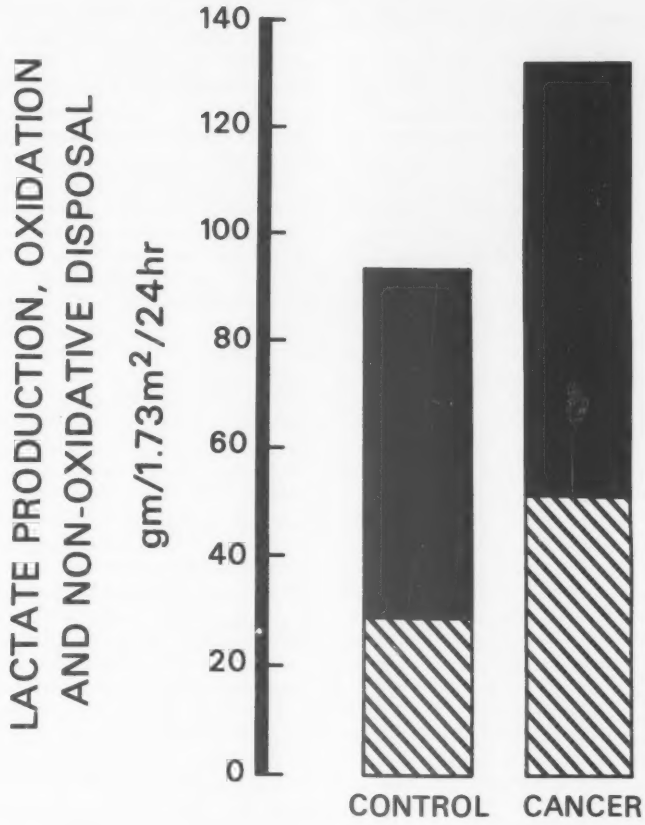

FIGURE 1.—Rates of lactate metabolism in 13 control subjects and 20 cancer patients. The height of the bars represents rates of lactate production. The black portion of each bar is the rate of lactate oxidation and the hatched portion represents nonoxidative disposal.

disposal, and the percent glucose derived from plasma lactate. This suggests that the quantitative differences between cancer patients and control subjects were primarily the results of enhanced rates of lactate production.

Surprisingly, the observed results correlated poorly with tumor burden and no correlation was observed between increased lactate production and a battery of clinical or biochemical determinants. It is inferred, but not proven, that the observed excess lactate production resulted in part from tumor glycolysis since increased anaerobic metabolism of glucose by human colorectal adenocarcinomas has been observed in vitro (23). These data show that while lactate production is increased, heterogeneity with respect to lactate metabolism exists, even within an apparently homogenous group of patients with a common solid tumor.

Because whole-body lactate production may be partly dependent on tumor glycolysis which may serve, therefore, as a measure of tumor activity, we have evaluated lactate metabolism before and at the completion of 4 weeks of chemotherapy with 5-FU and hydroxyurea in ten patients with colorectal cancer. In the one patient who achieved an objective tumor response, a 50% decrease in lactate production occurred while no significant effect on lactate metabolism resulted from chemotherapy in nonresponding patients. Of interest, a moderate (mean, 10.4%) reduction in O_2 consumption was observed in all patients. Although no firm conclusions can be reached from this small study in which dietary factors were not evaluated, the possibility ex-

ists that chemotherapy may directly affect host-energy expenditure.

Despite direct and indirect evidence of increased lactate production in patients with cancer, only sporadic reports of the association of lactic acidosis with malignancy have appeared in the medical literature. This uncommon, yet well recognized syndrome, has most often been described in association with disseminated hematologic malignancies where it can occasionally be reversed by successful antineoplastic therapy and appropriate supportive measures (24). More recently, lactic acidosis has been reported in some patients with uncontrolled solid tumors, such as bronchogenic carcinoma and hepatocarcinoma (25). The precise metabolic events that lead to the development of lactic acidosis are, however, not known. It seems probable that the simultaneous occurrence of increased lactate production with decreased lactate clearance through direct or remote mechanisms is required.

The recent description of a case of reversible lactic acidosis induced by total parenteral nutrition (TPN) in a patient with a bulky pelvic tumor (26), is of contemporary interest. With the advent of TPN as an established therapeutic modality, increasing use of this technique for the nutritional support of cachectic patients has resulted. Since TPN alters the metabolic and biochemical profile of even normal subjects, it is not surprising that significant changes may occur in tumor-bearing patients.

Plasma lactate concentration normally rises in response to glucose loading and we (27) and others (26) have described moderate lactic acidemia in cancer patients during TPN administration with solutions of hypertonic glucose and amino acids. Because venous plasma lactate correlates directly with the rate of lactate production in the basal state (22), increased lactate formation during TPN seems probable, but remains to be proven by direct measurements.

Following exogenous glucose administration to normal humans, the behavior of the blood glucose concentration is a reflection of a decreased rate of endogenous production and an increased rate of utilization (or disappearance) of glucose. The abnormal glucose tolerance observed in diabetic (28) and septic (29) patients is due in part to the lack of suppression of endogenous glucose production. In such patients, basal endogenous glucose production and gluconeogenesis may be increased in a manner similar to that observed in cancer patients with progressive weight loss (16). Rates of glucose production and utilization have not been measured in cancer patients following a glucose load, but have been determined during TPN when large quantities of glucose are continuously administered (27). In these studies, cancer patients with progressive weight loss and with normal or enhanced rates of glucose turnover and Cori cycle activity responded to TPN with marked decreases in rates of endogenous glucose production and increases in rates of glucose oxidation. The observation that gluconeogenesis may be suppressed in such patients has recently been confirmed by the finding that alanine conversion to glucose was decreased following the administration of even small quantities of glucose (30).

In response to TPN, glucose oxidation rates increased in proportion to the rates of glucose administration. Generally, over 50% of the glucose administered was immediately oxidized, accounting for about 50% of the total energy expenditure of the patient. Similar results have been obtained in burned (31) and traumatized (32) patients receiving TPN. In addition, glucose and insulin concentrations rose, as anticipated, and free fatty acid concentrations decreased (27). In common with cancer-free patients, values for respiratory quotient (RQ) rose to >1.0 as CO_2 production increased significantly and O_2 consumption (and hence caloric expenditure) increased moderately. Despite the suppression of gluconeogenesis with achieved RQ values >1.0, sustained weight gain and reversal of nitrogen catabolism may, as pointed out by Nixon et al (33), fail to result from TPN in the presence of uncontrolled malignant disease. While the reasons for this failure remain obscure and the potential benefits of TPN in cancer cachexia are a matter of current controversy, it is evident that parenteral nutritional support may cause profound metabolic changes in a condition for which our understanding is limited.

In this review, we have attempted to outline the known abnormalities of glucose and lactate metabolism associated with the syndrome of cancer cachexia. It is clear that many or possibly all of these abnormalities may not be specific to the cancer-bearing patient. Much additional information is needed in carefully defined groups of cancer patients to improve our understanding of this complicated syndrome. It would be helpful for example, to define the relationship between abnormalities of carbohydrate metabolism and anorexia. Since the forced feeding of animal tumor models may accelerate tumor growth at the expense of host metabolism, the possibility that anorexia represents a protective homeostatic mechanism must be addressed. Lastly, potentially useful nonchemotherapeutic agents may be able to ameliorate abnormal host metabolism. Future investigation of the use of such agents with particular reference to both subjective as well as objective changes in the patient may prove to be worthwhile.

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Oxidation and Metabolic Interconversion in Malignant Cachexia[1]

Christine Waterhouse[2,*]

SUMMARY

Some patients with progressive malignant disease have an increase in basal metabolic expenditure as well as total caloric expenditure, but the findings are neither striking nor consistent. Studies of specific metabolic changes in such patients have shown the following. (*a*) The predominant substrate for energy in these subjects is fatty acid, as in normal humans. Comparative studies show, however, that greater proportions of the oxidative metabolism in patients with cancer are from fatty acid, particularly when exogenous glucose is available. While the free fatty acid levels in plasma decrease appropriately with glucose administration, current evidence suggests that the levels of free fatty acids themselves may not necessarily be directly related to the various disposal mechanisms. (*b*) Increased glycolysis and gluconeogenesis are present after overnight fasting in patients with malignant disease, but these processes, which depend on liver metabolism, are appropriately suppressed with exogenous glucose. (*c*) Evidence is presented that leucine, an amino acid representative of branched-chain amino acids, is not under normal metabolic control in these subjects. For example, semistarvation does not result in diminished levels of branched-chain amino acids as it does in other patients. Also, glucose does not have its ordinary suppressive effect on branched-chain amino acid levels. Leucine turnover is increased in these patients as is the percentage of leucine flux which is oxidized. Limited data support the thesis that glucose does not suppress leucine flux normally, nor does it suppress the oxidation of this amino acid. All these data suggest that the peripheral effects of insulin and glucose may not be normally mediated in these subjects. They also suggest that amino acid metabolism and consequently protein metabolism may be unaffected by normal control factors in malignant disease.

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It has become increasingly clear that it is essential to define the stage of malignant disease to properly interpret any metabolic study. Many patients with cancer, even those with metastatic disease, remain well nourished and have no anorexia or weight loss. The main thrust of this report is not directed toward these patients, since our major interest has been the mechanism of malnutrition in progressive cancer. Since relatively new techniques have been used, studies in control subjects are important as a reference point for metabolic study in patients with malnutrition from cancer. For controls, some authors have chosen patients with cancer who show no evidence of body wasting (1), while others have chosen patients without malignant disease who have weight loss comparable to that seen in patients with carcinoma (2). Both approaches have merit, but one might expect somewhat different comparative results since semistarvation itself will result in certain metabolic changes.

The problem of overall oxidative metabolism or total energy expenditure is difficult to study. Not only do we have large inherent variations in the normal population, but our methods of measurement are also quite imprecise. Even the mesurement of resting metabolic expenditure, which in theory should be easily measured with our current technology for O_2 and CO_2 concentrations, is quite dependent on the ability of the

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patient to maintain normal ventilation under somewhat constrictive conditions. Studies of 24-hour metabolic expenditure are even more indirect and require more assumptions.

In addition to these methodological problems, all such data must be considered in the context of the cancer patient's clinical course. In spite of anorexia, weight loss, and tissue wasting in these subjects, the clinical course of the patient with cancer is often distressingly chronic. The sudden catastrophic changes usually associated with infections, burns, and severe trauma are usually absent, thus we are dealing with metabolic changes that may be small in relation to control mechanisms.

Nevertheless, studies have been done on this problem and can briefly be summarized as follows. Basal metabolic rate as determined by oxygen consumption in a group of subjects with progressive cancer and malnutrition showed that roughly half of the subjects had values considered to fall within normal range (3). The other half fell outside, being > 20% above the mean value. Total daily caloric expenditure as determined by the method of insensible weight loss was >60% above the basal energy expenditure for 9 of the 12 subjects (4). Studies by Holroyde et al (1) estimating caloric expenditure by indirect calorimetry have compared patients with cancer and progressive weight loss to subjects with cancer who had no weight change. There was no significant difference between the two groups, with the resting caloric expenditure for the control group being 33 k/cal/m²/hr and that for the group with cancer and progressive weight loss being 37 kcal/m²/hr (1). The slightly higher figure for the weight-loss group was due to quite high values in three deviate subjects. The most recent work in this area is that of Warnold et al (6), who used the heart rate method for energy expenditure. They found that both the daily energy expenditure and the resting metabolic expenditure were significantly greater in patients with cancer cachexia than in subjects who had similar degrees of cachexia but due to other processes than cancer. Their mean values were rather striking, daily energy expenditure being 2020 kcal/24 hr in cancer patients and 1420 for the controls. The resting metabolic rate was 1630 kcal/24 hr versus 1170 kcal/24 hr for the control group. Again there was overlap in the control and cancer groups. It is of some interest that both resting metabolic rates and total daily expenditures were elevated, whereas in earlier studies the predominant difference was in total daily expenditure.

In sum, probably some, but certainly not all patients with progressive carcinoma, have measurable increases in oxidative metabolism. More definitive studies in this area seem unlikely in the near future because of our methodological problems. Meanwhile it seems quite reasonable to study certain areas of metabolism in these patients that might result in an increased energy expenditure. Small changes in overall expenditure may be the result of major changes in specific metabolic processes.

Certainly the greatest proportion of our energy is derived from the oxidation of fatty acids, and some studies of fatty acid metabolism have been carried out in the patient group of interest to us. Slightly greater amounts of free fatty acid were oxidized to CO_2 in patients with progressive malignant disease than in control subjects in the overnight fasting state (6) (fig 1), but the difference was not statistically significant. Flux of labeled free fatty acid into the circulation was the same in the two groups. Glucose administration produced a comparable reduction of influx of fatty acids into the circulation but a much higher percentage of the label was found in CO_2 in subjects with malignant diseases, a finding that implies a drain on fatty acid stores for oxidative purposes.

One of the questions that arises is whether the continual use of fatty acids for oxidation when another energy substrate is available is a result of remodeling of substances prior to oxidation. This would be an expensive metabolic process. If, for example, the two-carbon fragments from glucose were shunted toward fatty acid synthesis rather than through the Krebs cycle, the ATP-energy requirement would be considerable. While in theory it should be possible to measure the incorporation of the labeled carbon of glucose into free fatty acids or the fatty acid and glycerol components of circulating triglycerides, studies to date have shown such low counting rates that the data have been useless. Probably this should have been anticipated since most of the free fatty acids in the circulation have been derived by lipolysis from the body fat stores, which would cause enormous dilution of label from any glucose uptake. Synthesis of fatty acids and glycerol in the liver for possible incorporation into circulating lipoproteins may well be a time-consuming process that is far longer than the length of our experiments. Recent studies by Bjorntoorp and Sjostrom (7) suggest a different approach to this problem and warrant further attention.

Another area of fatty acid metabolism relative to lipolysis in peripheral tissues has also been investigated. Our early studies showed that the plasma and free fatty acid levels after a 15-hour overnight fast were identical to those in the normal population. Dietary manipulation prior to the overnight fast has been shown to be a factor in such levels and previous high carbohydrate intake dropped the levels in the normal group from 0.6 mEq/liter to 0.3 mEq/liter. A similar change was found in the subjects with malignant disease (8). The effect of acute glucose loads on plasma free fatty acid levels and on free fatty acid flux into the plasma has been studied both in mice (9) and in

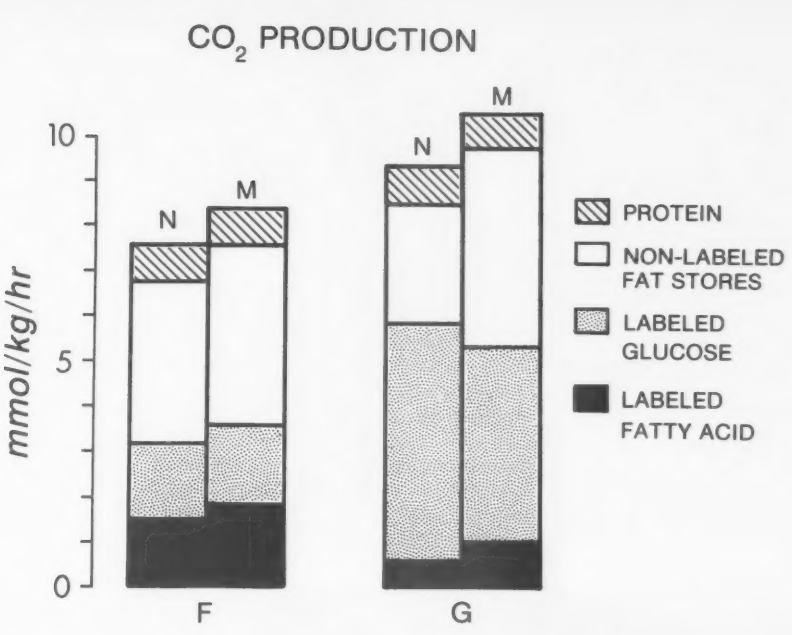

FIGURE 1.—Sources of CO_2 production in control subjects (N) vs patients with malignant disease (M) in the overnight fasting state (F) and during exogenous glucose feeding (G).

human beings (6). In both species glucose feeding resulted in equivalent decreases in free fatty acid levels and in free fatty acid flux into the plasma. The reduction was about 50% in both the animal and human studies (table 1). Thus it appears that normal control mechanisms for inhibiting free fatty acid mobilization following ingestion of carbohydrate are intact in subjects with malignant disease.

It has become clear, however, that the endogenous fat mobilization and utilization may not necessarily be estimated by circulating levels of fat-derived substances, including free fatty acids. For example, the administration of 2 g/kg/day of amino acids to patients results in a positive nitrogen balance at glucose, insulin, glycogen, and free fatty acid levels not different from those receiving 1 g/kg/day (10). The caloric deficit in this instance must have been met by exogenous fat mobilization, even though the free fatty acid and ketone body levels were not significantly elevated. This requires some equivocation concerning the interpretation of free fatty acid levels by themselves.

TABLE 1.—Plasma concentrations FFA

	Fasting mEq/liter	With glucose mEq/liter
Cancer	0.58 ± 0.03	0.30 ± 0.04
Normal	0.57 ± 0.05	0.23 ± 0.01

Studies pertaining to interconversion and oxidation of carbohydrates were considered by other speakers. However, two points in this area directly bear on the problem of overall oxidative metabolism and should be briefly considered.

The flux of glucose into the circulation or the direct input of new glucose molecules in the overnight fasting state is accelerated in patients with progressive malignant disease (12). The recycling of glucose through lactate and pyruvate is also increased (1,11). Oxidation of glucose resulting in labeled CO_2 production accounts for only about 50% of the irreversible egress of glucose molecules (6). A critical area for study would be the fate of the glucose molecules that are not oxidized. It seems highly unlikely that glycogen is being synthesized during the overnight fasting state. Some fatty acid synthesis probably occurs continually, but quantitatively should not be very significant under this condition. There has been considerable recent interest in glycoprotein substances in cancer patients and possibly this would constitute another fruitful area for study.

The second point for consideration in this area concerns gluconeogenesis and the studies of alanine to

glucose conversion (2). The ^{14}C label from alanine is found in increased quantities in circulating glucose in subjects with carcinoma. Such data have in the past been considered evidence for gluconeogenesis and the use of carbon atoms derived from amino acids for glucose synthesis. Recent studies of interconversion of alanine and glucose, however, suggest the opposite conclusion. Indeed, far more carbon atoms from glucose are converted to alanine carbon than are resynthesized back into glucose. While increased recycling of glucose both through pyruvate and alanine may require extra energy, it would hardly appear that this is a drain on protein stores.

Finally, I would like to discuss certain recent studies of ours and others related to amino acid and protein metabolism. Unless complicating factors exist, nitrogen wastage as evidenced by excessive urinary nitrogen is usually absent. Recent studies of plasma amino acid levels and arteriovenous differences across the forearm muscle tissue have shown that there is no excessive drain of amino acids from muscle tissue, though some caution in interpretation of AV difference is in order (12). Relatively old studies concerning albumin synthesis have shown similar iodinated albumin decay curves in patients with metastatic cancer as were found in patients with semistarvation (13). Since the serum albumin levels were low, this indicates diminished synthesis of albumin. Thus overall nitrogen conservation and appropriate diminished synthesis of certain nonessential proteins seem to indicate normal adaptation to a substandard protein intake. However, other evidence suggests that protein turnover may actually be increased in certain areas. We have presented evidence for increased turnover of immunoglobulins triple the normal value in this state at times (14). Others have shown in vitro that impaired synthesis of muscle protein may be overcome by an increased supply of amino acids (15). The recent evidence for urine excretion of glycoproteins suggests increased synthesis in this area (16). In a study of pre- and postoperative protein metabolism, as measured by ^{14}C-leucine turnover and oxidation (17), O'Keefe calculated about a 50% increase in leucine flux in a patient with metastatic carcinoma versus three other subjects who did not have cancer. The urinary urea output as similar to that of other subjects. The calculated protein synthesis from leucine was about 30% higher than that of the other subjects, while the protein breakdown was about 100% greater. Finally, the amino acid levels in patients with semistarvation and cancer have shown that the branched-chain amino acid levels remain within normal limits (12), while those from patients with other types of starvation are characteristically reduced after a relatively short period of time (3–5 days). Interpretation of this finding is not possible without further information. However, comparison of a longitudinal study of a patient with cancer versus one with anorexia nervosa at comparable percentage loss of body weight makes it unlikely that this finding is related to differences in the evolution of the malnutrition (table 2).

It should be noted that for the most part the branched-chain amino acid levels were not increased in the malnourished subjects with cancer, but simply remained within the normal range. Thus, attempting to compare these levels with the increased levels of branched chains that are seen in uncontrolled diabetes mellitus, nonketotic trauma, and exercise may not be entirely valid. In some of these states there is increased catabolic activity within the muscle cell, but not always. In some situations there is no increase in 3-methylhistidine excretion (18), and in vitro muscle studies indicate decreased synthesis of muscle protein rather than increased catabolism. States of increased gluconeogenesis are usually associated with elevated branched chain amino acid levels and perhaps that is one factor that is operative here. We also suggest the possibility of increased reutilization of amino acids within the liver for the purpose of increased protein synthesis.

In a study of whole blood amino acid levels in patients undergoing parenteral alimentation, we estimated by bivariate regression analysis the anticipated rise in each amino acid with the infusion of 1 mmol/hr of that amino acid and the change in the amino acid with the infusion of 1 mmol/hr of glucose (19). The subject group of 25 contained 7 patients with progressive malignant disease. When this group was separated from the rest, the data showed less rise in the branched-chain amino acids in patients with malignant disease than they did in the rest of the subjects. For example, with the infusion of 1 mmol/hr of leucine the subjects without cancer had a rise of 53 μmol/liter whereas the subjects with malignant disease had a rise of only 13 μmol/liter (table 3). Perhaps of even greater significance was the fall in the branched-chain amino acids when glucose was given to the subjects without malignant disease and the rise in the group with cancer. Thus the patient with progressive cancer has a good and probably a better capability of branched-chain amino acid handling as is seen with other types of malnutrition. The fall in branched-chain amino acid levels with glucose administration in normal subjects

TABLE 2.—Plasma leucine (μmol/liter)

	% of normal body weight		
	100%	85%	70%
Anorexia nervosa	140	132	102
Progressive cancer	134	134	154

TABLE 3.—Amino acid levels with parenteral infusion

	Normal		Malignant disease	
	(Δμmol/liter with 1 mmol/hr infusion)			
	Amino acid	Glucose	Amino acid	Glucose
Valine	+144	-1.50	+57	+0.46
Isoleucine	+ 48	-0.48	+46	-0.05
Leucine	+ 53	-0.59	+13	+0.57

has been shown by others, and at least part of this effect is attributed to increase in insulin levels. The failure of the subjects with malignant disease to lower their branched-chain amino acid levels with glucose ingestion might suggest insensitivity of muscle protein catabolism to the normal control factors of glucose and insulin.

Because of the above findings we have chosen leucine as representative of the branched-chain amino acids for study in control subjects and patients with malignant disease. Like all the other amino acids we have studied thus far, ^{14}C-leucine disappears very rapidly from the blood stream. The flux of leucine is about 80–100 μmol/kg/hr in a group of control subjects with some degree of malnutrition (table 4). Similar studies in patients with progressive malignant disease showed values roughly 40% higher than this. With glucose administration most of the control subjects showed a decrease in leucine flux while those with malignant disease still had high values.

The appearance of the labeled carbon in CO_2 when leucine is given is very rapid, but also sustained over a prolonged period of time. The physiologic meaning of this is not readily apparent. Certainly the very rapid appearance of labeled carbon in the expired air implies a rapid oxidation of certain leucine molecules. The persistent feeding of label to the bicarbonate pool over a long time could be related to sequestering and slow release of leucine, or it could be from reprocessing of this amino acid and later oxidation. It seems unlikely that any synthesis into protein followed by degradation could be responsible, but perhaps reprocessing to fatty acid and later oxidation is a possibility. In contrast to the gluconeogenic amino acids, relatively small amounts of the carbon skeleton of leucine appear in CO_2. Our data show an average of about 20% of the leucine flux is eventually oxidized. This correlates quite well with the data of Golden and Waterlow (20). This relatively small oxidation is undoubtedly related to the fact that the liver plays a very small role in oxidative metabolism of leucine. Patients with progressive malignant disease appear to have an increased oxidative metabolism of leucine, with perhaps 30%–40% of the flux being oxidized (table 5). With glucose administration the oxidation of leucine was decreased in the control subjects, but remained quite high in some subjects with malignant disease.

TABLE 4.—New leucine production rate (μmol/kg/hr)

	Overnight fast	With glucose
Control (6)	88 ± 3	77 ± 7
Malignant disease (5,3)	145 ± 6	145 ± 22

TABLE 5.—Leucine oxidation (% injected dose)

	Overnight fast	With glucose
Control (5)	19.1 ± 2.2	14.8 ± 1.7
Malignant disease (5,3)	34.0 ± 2.2	26.5 ± 9.5

Attempts to measure protein synthesis by the appearance of the ^{14}C label in circulating proteins has shown that about 10% of the ^{14}C-leucine label eventually appears in circulating proteins in the control subjects, and there is not much difference in patients with malignant disease. Isolation of albumin for its radioactive carbon content perhaps showed a borderline low value as compared to control subjects, but there was no statistical significance between the two groups.

In summary, our studies confirm the increased flux or turnover of leucine in subjects with malignant disease, a somewhat increased oxidation of this amino acid, and a failure of these parameters to be normally suppressed by glucose administration. We have not yet found any difference in the incorporation of radioactive leucine into circulating proteins, but obviously what is needed is a breakdown of such data into specific classes, such as glycoproteins and acute phase proteins as well as the γG immunoglobulins. It is our feeling at the moment that increased activity in the area of amino acid metabolism and its interconversion with other substances may well constitute a drain on limited energy resources.

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Nitrogen Metabolism in Cancer Patients

Murray F. Brennan* and Michael E. Burt[1]

SUMMARY

The methods of examining nitrogen metabolism in cancer-bearing humans are examined with specific examples. The major nutritional effect of cancer on the host is lean tissue and caloric reserve dissolution, with increased total body water. It seems clear that gluconeogenesis from amino acids can be suppressed by exogenous substrate. With appropriate nutritional repletion, protein catabolism can be suppressed and synthesis stimulated.

[Cancer Treat Rep 65 (Suppl 5):67–78, 1981]

A number of methods exist for the study of protein and amino acid metabolism in cancer (table 1); most are directed to examination of the contained nitrogen.

NITROGEN BALANCE STUDIES

Nitrogen balance studies are, at best, difficult to interpret. Nitrogen equilibrium, nitrogen loss, and nitrogen retention have all been variously reported without clear delineation of energy requirements or weight change of the host (1,2). Carefully done studies in our own and other laboratories have suggested that under the influence of total parenteral nutritional support (TPN), positive nitrogen balance can be obtained in most severely malnourished patients with an intake in excess of 1575 nonprotein calories and 12 grams of nitrogen (figs 1,2). In these studies, pre-TPN nitrogen balance was negative, and the patients had lost an average of 18% of their pre-illness body weight. The basic objection to the use of nitrogen balance studies has been the difficulty in maintaining "steady state" for 2 or 3 days, to allow for meaningful intake and output. In addition, the study is so dependent on the com-

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TABLE 1.—Methods for examining nitrogen metabolism in cancer-bearing humans

Whole body changes
Nitrogen balance
Total protein flux (stable and radioactive isotopically labeled proteins and amino acids)
Body composition (stable and radioactive isotopic studies; neutron activation analysis of nitrogen)
Amino acid kinetics (amino acid disposal, interconversion)
Compartmental analysis (electrolytes, fat, nitrogen)
Mineral balance (K, P, Mg)
Tissue and organ changes
Specific protein synthesis rates
In vitro protein synthesis
Limb flux of amino acids, in vivo and ex vivo
Tumor biopsy studies
"Marker" studies
Plasma proteins
Plasma and urinary amino acids
3-Methylhistidine
Polyamines

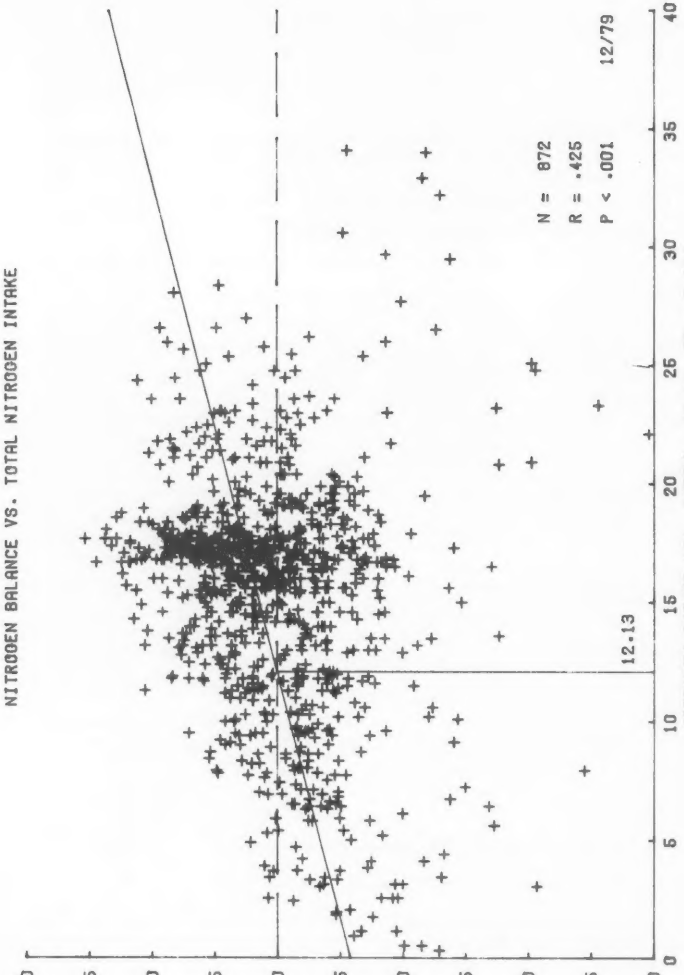

FIGURE 1.—Nitrogen balance as a function of total nitrogen intake during TPN, based on total urinary nitrogen determinations. Patients with fistulae, significant stool, diarrhea, or skin desquamative disorders, are excluded.

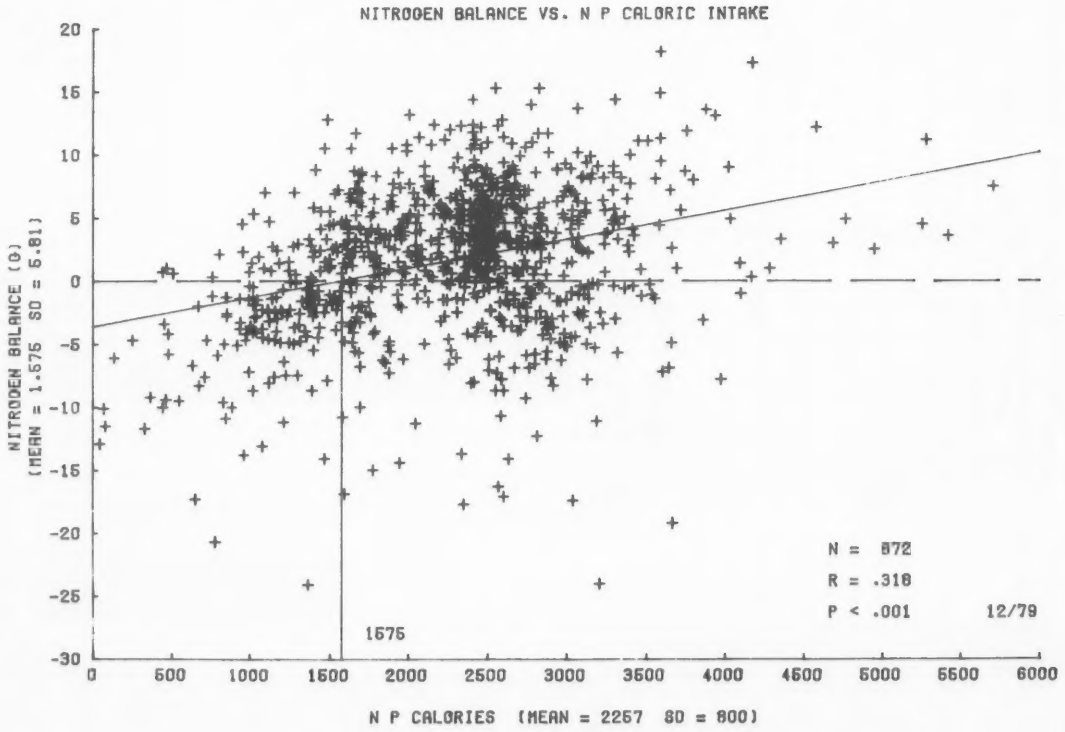

FIGURE 2.—Nitrogen balance as a function of nonprotein caloric intake.

pleteness of collections that routine clinical usage is impractical.

The clinically applicable urinary urea nitrogen determination, with a correction factor, has been widely employed as an alternative. This would appear adequate in the not totally starved cancer patient whose "other" losses from stool, fistulae, etc are usually small. In patients who have been chronically starved, the urinary urea nitrogen is small, and total urinary nitrogen must be measured to include the large percentage of urinary nitrogen lost as ammonia.

WHOLE BODY PROTEIN FLUX STUDIES

Protein turnover in mammalian tissues and in the whole body has recently been reviewed by Waterlow et al (3). They have used the concept of whole body protein turnover to be analogous to total oxygen uptake, both determinations being the sum of changes that exist in various cells and organs that differ widely in their metabolic rates. It should be emphasized that both protein synthesis and catabolism are energy-requiring processes. Therefore, the protein turnover that occurs, even in a steady-state situation, represents considerable energy expenditure.

Basic assumptions are taken in estimating total protein turnover. A steady-state situation is assumed and the flux of a specifically labeled amino acid or its metabolites into and out of body protein pools is examined. Studies using these methods in cancer-bearing humans are somewhat limited (4).

An example of a study utilizing ^{15}N-glycine to determine nitrogen turnover in a patient with esophageal cancer prior to and following TPN is illustrated in figure 3. Figure 4 illustrates nitrogen balance in this patient. Prior to TPN, the patient is in negative nitrogen balance and has a nitrogen flux of approximately 350 mg/kg/day. Catabolism exceeds synthesis, and this is reversed by TPN. After 2 weeks of TPN with weight gain, the nitrogen balance is reversed and becomes positive, total nitrogen turnover increases by 68%, with synthesis increasing 74% and catabolism be-

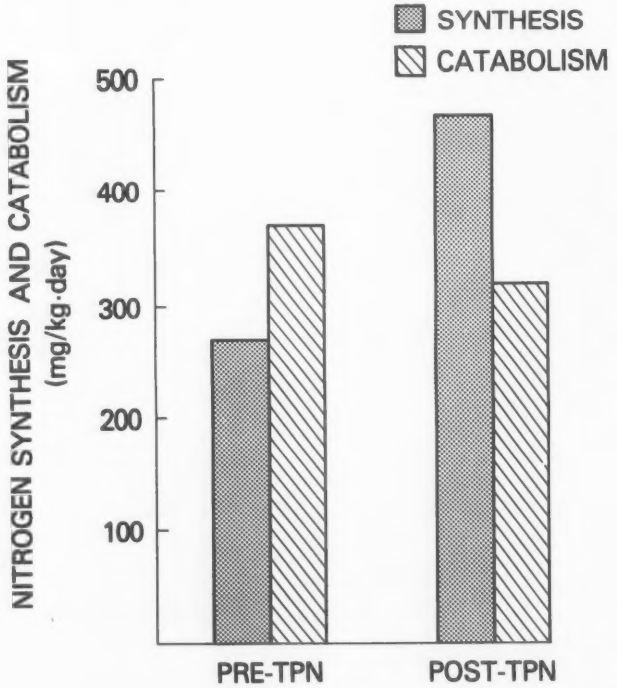

FIGURE 3.—Whole body nitrogen synthesis and catabolism in a patient with localized esophageal squamous cell carcinoma, as measured by ^{15}N-glycine (24-hour constant infusion), before and 2 weeks following total parenteral nitrogen (TPN) (Burt ME, Stein PF, Brennan MF. Unpublished observations).

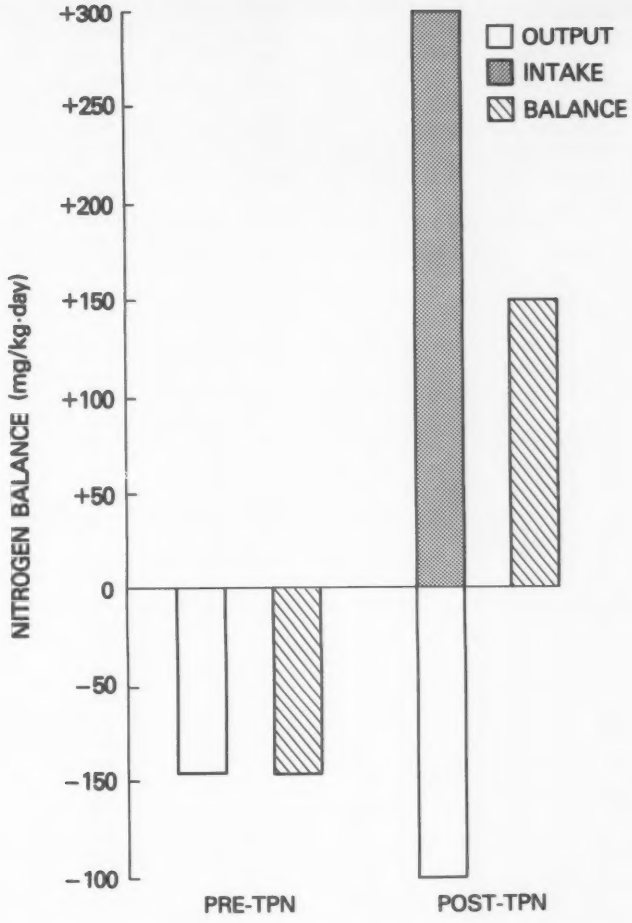

FIGURE 4.—Nitrogen balance during the same two 24-hour periods for the patient described in figure 3.

ing diminished 13%. These changes are associated with a marked increase in insulin (4–43 μU/ml), and a mild decrease in glucagon (142–117 pg/ml).

In a study of six patients with metastatic adenocarcinoma in the liver, studied before and after 1000 r of radiation to the liver in conjunction with 5-FU therapy via the intrahepatic artery, Blackburn et al (5), using constant infusion of ^{14}C-leucine, found no significant decrease in protein breakdown (3.84 ± 0.37–3.44 ± 0.34 mg/leu/hr), but a significant decrease in synthesis (3.29% ± 0.33%–2.77% ± 0.32%), with a significant increase in the percent of flux oxidized to CO_2 (14.5% ± 1.7%–19.7% ± 2.4%). Such studies emphasize the need to promote synthesis as well as inhibit catabolism.

BODY COMPOSITIONAL STUDIES

Body compositional studies directed at examining protein metabolism have depended mainly on the examination of total exchangeable sodium and potassium (Na_e/K_e). These are measured by the dilution of appropriate isotopes of the two ions. Assumptions are made as to equilibrium and distribution, and specific activity is determined. The amount of total exchange-

able potassium is effectively the total body potassium. Given that most potassium is intracellular, it is an indicator of cellular mass. The total exchangeable sodium, however, is not an indicator of total body sodium because of the large amount of sodium in the skeleton, which is either not exchangeable or very slowly exchangeable. In starvation unrelated to cause, body compositional changes appear such that lean tissue and fat are lost and water is retained. The plasma volume is large, the red cell volume is small, the hematocrit is low even though hyponatremia, hypoproteinemia, and hypotonicity exist (6).

In an early study of a patient just prior to her death from extensive Hodgkin's disease involving the stomach, Moore found a virtually unique situation of overhydration. The total body water was 77.5% of the total body weight, thereby effectively suggesting (by calculation) that no body fat remained! The body cell mass was small. The patient, although not having had any known hemorrhagic loss, had an extremely low hematocrit with a very large plasma volume and a small red cell volume. Virtually all the muscle mass had been previously utilized (fig 5) (6). Other studies have shown similar changes (7). Warnold et al (8) recently summarized body compositional studies done on cancer patients and contrasted them to healthy controls. Again, in contrast to healthy controls, patients are shown to have a diminished body weight, body cell mass (table 2), and a diminished body fat in the presence of a relatively expanded extracellular water. Given that the cancer patients had lost weight, the total body water was expanded (34%-36% of body weight in patients, 29%-32% in controls), a further indicator of the insult that the body stores had undergone.

Total body potassium determinations using the stable isotope potassium 40-have revealed similar changes. Some patients with cancer undergoing TPN can increase their total body potassium by K^{40} scans (fig 6). It should be emphasized that such dramatic results are only seen in patients severely depleted prior to nutritional support. In patients relatively well nourished, the K^{40} will change little, as the body weight increase is consistent with increasing body fat, according to unpublished data by Popp et al.

BODY COMPOSITION BY NEUTRON ACTIVATION ANALYSIS OF NITROGEN

Recent reports have confirmed the validity of measuring in vivo body protein based on determination of nitrogen by prompt gamma analysis (9). The system

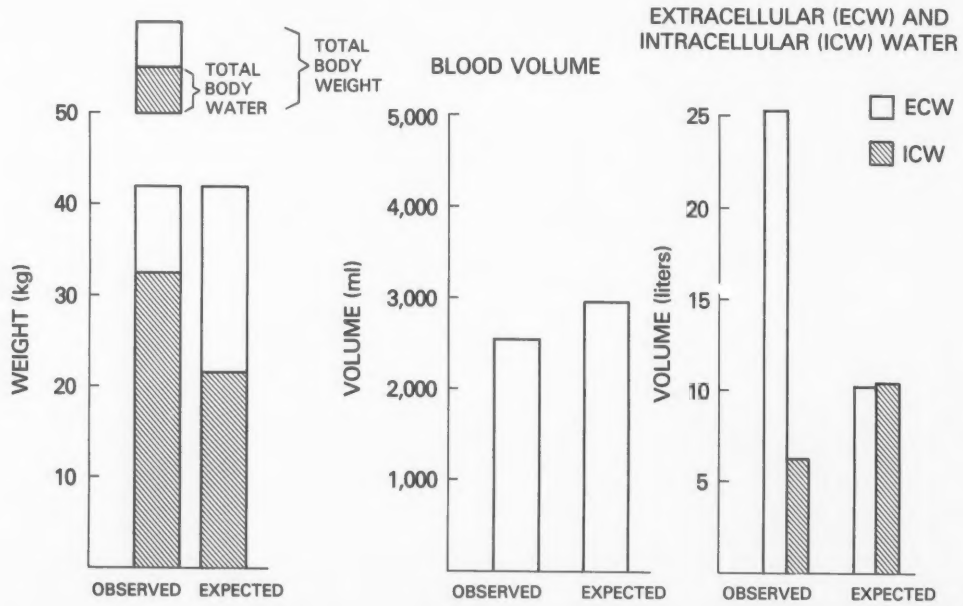

FIGURE 5.—Body composition of a patient with terminal Hodgkin's disease (observed) compared to the expected composition of a normal patient of same weight (6).

TABLE 2.—Body composition in cancer patients

	n	BW* (kg)	BCM† (kg)	ECF‡ (kg)	BF§ (kg)
Male patients	10	66.8±12.8	23.8±4.7	23.0±4.1	11.0±6.4
Healthy controls	100	76.2±10.9¶	29.0±3.9¶	24.9±4.8	13.0±5.6
Female patients	19	52.6± 9.4	18.2±2.6	17.9±4.0	9.0±8.0
Healthy controls	64	66.5±12.5¶	20.2±2.7¶	19.6±4.3¶	18.6±7.3¶

* BW = Body water.
† BCM = Body cell mass.
‡ ECF = Extracellular fluid.
§ BF = Body fat.
¶ $P < 0.05$ in patients versus controls.

Data from Ref (8)

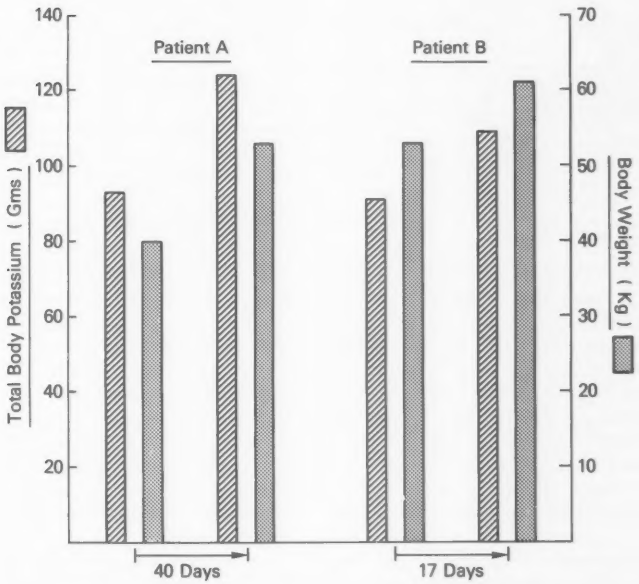

FIGURE 6.—Total body potassium as determined by ^{40}K total body counting in two patients before and after 40 (patient A) and 17 days (patient B) of TPN. Both patients received TPN, following surgical and chemotherapeutic tumor "debulking" of testicular cancer. Also shown is the total body weight.

depends on the principle that whereas 99% of body nitrogen exists as the stable ^{14}N isotope, with the capture of a neutron ^{15}N may be formed in an excited state, and this immediately decays to a stable ^{14}N in 14% of cases with emission of a gamma ray of 10.8 MeV. This radiation is uniquely characteristic of nitrogen, and the number of gamma rays produced at 10.9 MeV is proportional to the amount of nitrogen present. An internal standard of activated hydrogen which emits a similarly characteristic gamma ray (2.2 MeV) allows a nitrogen to hydrogen mass to be determined, once a calibration factor is obtained by a subsidiary experiment using a body-sized phantom containing a known amount of urea dissolved in water. Then, using a "known" fraction of the body mass that is hydrogen, the mass from nitrogen may be obtained. While assuming uniformity of nitrogen and hydrogen throughout the body introduces an error, it is presumably small. Using such methods and validating them by chemical analysis of pig carcass, similar results have been obtained (9). One outcome of this analysis was that the good correlation of nitrogen to potassium ($r = 0.87$)

had, however, a wide variation about the regression line. This suggests that the calculated value for total body nitrogen from a total body potassium value would be subject to some variability. While in male volunteers the N/K ratio was 12.5 ± 1.5 g/g, and in women, 14.4 ± 2.2 g/g, there was wide variability when patients of various malnourished states were included in the analysis.

With all subjects the N/K values varied from 7.5 to 20, consistent with the wide variation between different tissue concentrations of nitrogen and potassium in the body. Such variations in nitrogen and potassium content may allow even a normal subject to vary from wide extremes of N/K ratio, depending on the percentage of muscle and fat. One observation from the neutron activation nitrogen analysis was that total body nitrogen and the square of height for both controls (normal and in hospital), was consistently correlated. The malnourished patients had a similar correlation, but in all cases had markedly less total nitrogen for height. Such attempts at correlation and the variability obtained emphasize our deficiencies in the accuracy of available determinations.

AMINO ACID KINETICS

Various authors have used gluconeogenesis from alanine to examine patients with progressive malignant disease (10). Using a single injection of ^{14}C-U-alanine (0.7 μCi/kg, specific activity 177.0 μCi/mmol) in cancer patients, both before and after 2 weeks of TPN, we have shown virtual complete suppression of alanine to glucose conversion (fig 7). The alanine pool, as expected, increased twofold with an approximately 100% increase in alanine turnover rate after 2 weeks of TPN. This is in agreement with the work of Waterhouse (10), who suggested that in patients with cancer receiving infusions of glucose, alanine to glucose conversion can be demonstrated to be diminished. The addition of TPN (containing both alanine and glucose) results in virtual abolition of alanine to glucose conversion, similar to that seen with controls (table 3) (10).

Meaningful studies of carcass analysis and mineral balance in cancer-bearing humans have not, to our knowledge, been performed.

PROTEIN SYNTHESIS IN SPECIFIC TISSUES (IN VIVO)

This subject continues to be an area of rapid development, although in the cancer-bearing host, very few studies have been published (4). Studies are somewhat crude, as they examine the total synthesis of an organ system that may contain a great number of cells of variable function. Examinations of tissues such as liver can be distorted because the variability between the normal percentage of parenchymatous functional cells (60%) is markedly diminished in diseases in which supporting and fibrous tissue make the greater proportion of the total cell number. No account can be allowed for rapidly dividing cells, such as gastrointestinal mucosal cells or bone marrow, and the organs that make protein for export provide special problems.

These studies are best performed by the constant infusion method to avoid the major errors introduced by reutilization. Data are usually expressed as fractional synthetic rate (FSR), which refers to a percent renewal per day. Such rates do not appear to depend on metabolic rate, and the relative overall metabolic rate of the heart and kidney has been estimated to be twice that of the liver and brain, which in turn is about ten times that of resting muscle. Protein synthesis rates of the liver and kidney are similar, however, while the heart is approximately 30% greater than muscle and about half that of the kidney (3). Because of the marked preponderance of skeletal muscle in humans, the muscle protein turnover will make a much more significant contribution to total turnover than in a small rodent. Consequently, data are occasionally expressed as absolute turnover rates.

In man, albumin makes up approximately 7.5% of total whole body synthesis rates, whereas muscle will make up approximately 50%; total protein synthesis in man is about 14 g per day (3).

TABLE 3.—Alanine-glucose kinetics during glucose infusion in man*

Patients	No.	Rate of infusion (mmol/hr)		Alanine to glucose conversion (mmol/hr)
		Alanine	Glucose	
Cancer	7	0	0	5.6±0.7
	3	0	55	1.0±0.2
	1	0	165	0.9
	3	0.6-1.8	82-165	0-0.8
Controls	7	0	0	2.5±0.2
	5	0	+	0.72±0.2

*Data from ref (10).

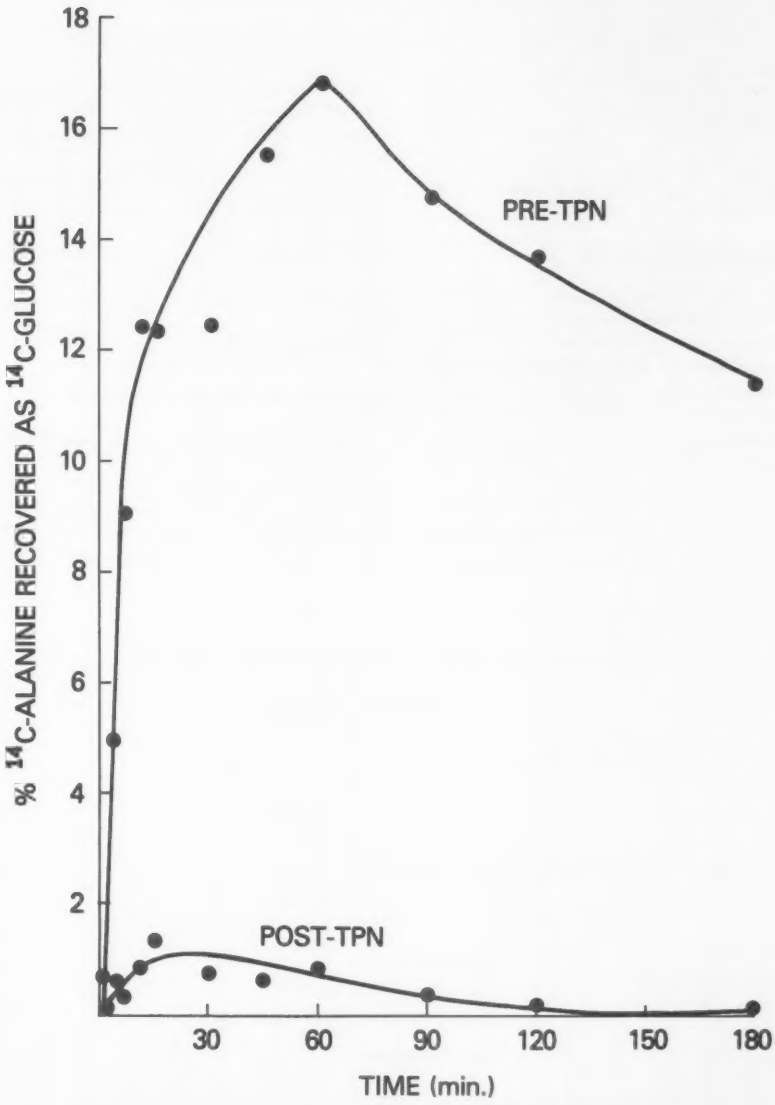

FIGURE 7.—Percentage of ^{14}C-alanine recovered as ^{14}C-glucose after a single injection of ^{14}C-U-alanine in a patient with localized esophageal carcinoma before and after 2 weeks of TPN.

Studies in tumor-bearing animals and man are minimal (4). Tissue amino nitrogen enrichment is a combination of intracellular and extracellular fluid amino nitrogen. These contributions have been considered to be 70% and 30% respectively (3). In these studies the ^{15}N enrichment of tumor tissue nitrogen was significantly greater but proportional to that of the corresponding normal tissue. Tumor protein synthesis rate in these

studies was slightly greater in proportion to the protein synthesis rate of the corresponding normal tissue. One problem of this method is that the experiments with ^{15}N-glycine reflect mainly the metabolism of nonessential amino acids. Calculations have been made to suggest that the rate of reutilization of nonessential amino acids is higher in nonmalignant tissues (54%) than in tumor tissue (34%) (4). This difference between tumor and normal tissue reutilization is consistent with the recurring hypothesis that the tumor tends to limit all activity in the direction of rapid growth.

PROTEIN SYNTHESIS (IN VITRO)

In vitro muscle protein synthesis has been examined by Lundholm (11) in 52 patients, all with advanced disease, who were fasted for 12 hours before operation. Controls were 72 healthy subjects. Samples were taken from liver and rectus muscle at the time of surgery. Cancer patients were shown to have decreases in skeletal muscle glycogen phosphorylase and glucose-6-phosphate dehydrogenase activity and increased hexokinase activity.

Leucine incorporation was increased in liver and decreased in muscle of cancer patients, consistent with increased gluconeogenesis. Specific examinations of individual proteins at a cellular level are limited in the main to autoradiography.

LIMB FLUX OF AMINO ACIDS

Examination of amino acid metabolism in vivo in the human extremity bearing a soft tissue sarcoma has clearly revealed that, at a time when the control (the tumor-free limb) is releasing amino acids consistent with the fasting state, the release of amino acids from the tumor-bearing limb is much less, and some amino acids are being taken up by the limb (fig 8) (12). This observation requires that determinations of flow be accurate and this has been validated by an ex vivo tumor-bearing limb model (13). Such models provide potentially exciting prospects for ex vivo perfusion of human tumor bearing extremities (14).

PLASMA PROTEIN CHANGES

Hypoalbuminemia is a common nonspecific occurrence in patients with cancer (15). The degree of hypoalbuminemia is usually correlated with the extent of the disease (16). The observations of a low serum albumin can be due to increased plasma volume, alteration in distribution of albumin between the intra- and

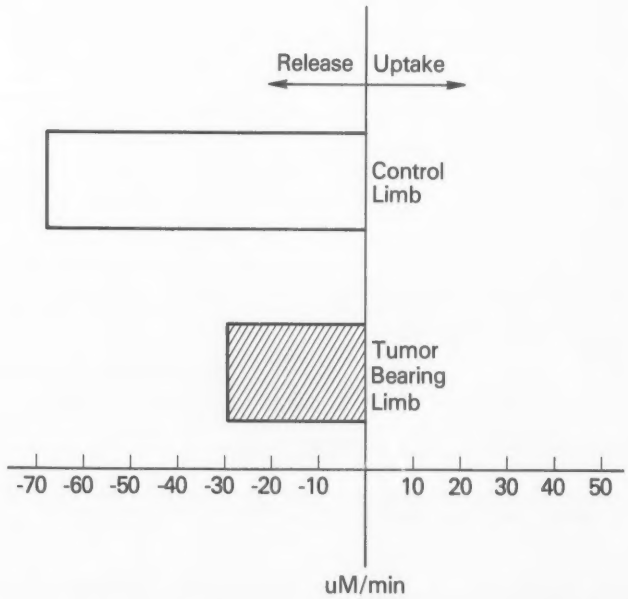

FIGURE 8.—Total amino acids released (μmol/min) from human sarcoma bearing limbs as compared with the contralateral (control) limb. Determined from arterial-venous concentration differences and blood flow by capacitance plethysmography (12).

extravascular space, decreased synthesis or increased catabolism of albumin, or any combination of the above.

Studies have shown that there is decreased albumin synthesis, normal catabolism, with decrease in total albumin pool, in the presence of low circulating albumin in the majority of cases (16,17). In some situations abnormalities of distribution clearly exist (eg, albumin in malignant effusions), such that the total body albumin pool may be increased, but these are uncommon. Similarly, in situations where protein-losing enteropathies exist (17,18), increases in the fractional rate of albumin catabolism can be demonstrated (table 4) (19,20).

TABLE 4.—Albumin kinetics in a patient with lymphoma and protein-losing enteropathy*

	Patient	Normal mean
Serum albumin (gm%)	1.9	4.1
Circulating albumin pool (g/kgm)	0.8	1.6
Albumin t-½ (days)	6.8	18±3
FCR (% of iv pool)	25	10.6±2

*Data from ref (17).

AMINO ACID MARKER STUDIES

Plasma and urinary amino acids have been poorly studied in cancer-bearing humans. Most recorded values reflect the effects of prior starvation or prior therapy. When patients are given TPN as part of a prospective randomized study of TPN in aggressive cancer chemotherapy for metastatic sarcomas, plasma amino acids can be compared, both to pretherapy levels and between TPN and no TPN groups (fig 9).[2] Major changes on TPN reflect the high content of glycine, alanine, and the mixture of D-L methionine. The branched-chain amino acids and phenylalanine increases in both controls and TPN-treated patients are consistent with the stress of aggressive chemotherapy.

Urinary hydroxyproline continues to be employed as a sensitive index of bone destruction in recurrent breast cancer and has been widely employed as an indicator of presence of osseous metastases from breast cancer (21). With careful attention to a restricted diet, clear elevations of urinary hydroxyproline in patients with metastatic breast cancer (by x-ray) can be demonstrated (table 5). In patients with negative x-rays, 20% had elevated urinary hydroxyproline. The latter group has been shown in other studies to have a high like-

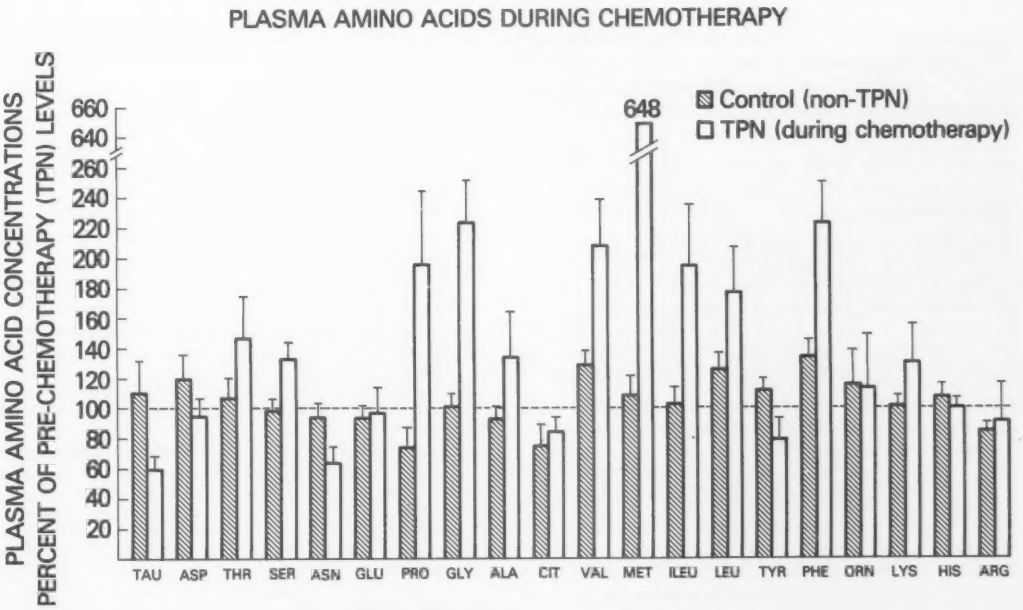

FIGURE 9.—Plasma amino acid levels in patients undergoing aggressive chemotherapy. Control and TPN levels compared to prechemotherapy levels (21).

TABLE 5.—Urinary hydroxyproline*

	Controls		Breast cancer†	
	μmol/24 hr/m²	(Hyp:creat)%	μmol/24 hr/m²	(Hyp:creat)
Study 1	94.7±7.4(28)‡	1.63	206.1±18.9(21)	5.58
Study 2	92.6±10.3(17)	1.64	247.9±32.0(14)	7.14

*Brennan MF, Lowry SF, Pizzo P, et al. Unpublished observations.
†Patients with positive x-rays for metastatic disease.
‡( ) = n

lihood of subsequently developing metastatic bony lesion from breast cancer (22).

Studies with 3-methylhistidine in human cancer have been poorly documented, mainly because of the failure to ensure controlled oral intake.

Since the polyamines (putrescine, spermidine, and spermine) have been correlated with cell growth, investigators have attempted to utilize the polyamines as markers of neoplasia. Fujita et al (23) determined the total urinary polyamines in 56 normal subjects, 2 pregnant women, 26 postpartum women, 72 tumor-free patients with a variety of diseases, and 54 patients with solid and hematologic malignancies. They found significantly greater total urine polyamines in the cancer patients than in either the normal subjects or tumor-free patients. Levels were also elevated in normal pregnancy. Rosenblum et al (24) demonstrated that the elevated level of polyamines is not secondary to decreased degradation. They administered ^{14}C-spermidine and ^{14}C-putrescine to normal subjects and patients with advanced cancer and found no difference in the plasma disappearance or urinary appearance rates.

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Metabolism in Peripheral Tissues in Cancer Patients[1]

K. Lundholm,* S. Edström, L. Ekman, I. Karlberg, and T. Scherstén[2]

SUMMARY

Cancer patients have increased insulin resistance in skeletal muscles and probably also in the liver. The insulin production in response to a glucose challenge is decreased. This is associated with decreased glucose uptake in peripheral tissues and increased gluconeogenesis from amino acids, lactate, and glycerol. The correlation between the insulin response to a glucose challenge and the activities of glycolytic and oxidative rate-limiting enzymes in muscle tissue suggests a common denominator for these metabolic alterations. The most prominent feature in alteration of lipid metabolism is a reduction of body fat, probably dependent on increased lipolysis. The released fatty acids are oxidized outside the tumor mass. Species characteristics may be important for the degree of hyperlipidemia. Wasting of the skeletal muscle mass is caused by decreased protein synthesis and probably increased degradation. Anorexia can induce but not entirely explain this altered protein metabolism. Decreased physical activity may be another important factor for the depressed protein synthesis. Total parenteral nutrition (TPN) improves the muscle protein synthesis. The mechanism behind increased fractional degradation of muscle proteins in vitro is not clear, but it may be coupled to increased cathepsin D activity.

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Cancer is often associated with impaired food intake, malabsorption of nutrients, decreased resistance to infections, altered hormonal balance, and low physical activity. These events may be responsible, directly or indirectly, for the metabolic alterations occurring in peripheral tissues of cancer patients and tumor-bearing animals. There is no conclusive evidence, as yet, that the tumor-host reactions in peripheral tissues are specific for the presence of a malignant tumor.

Studies of tumor-host reactions have been done in a variety of experimental animals with spontaneously developed or chemically-induced malignant tumors. Only sparse information is available on specific organ derangements in cancer patients. Results obtained in metabolic studies of tumor-bearing animals are not necessarily representative for the metabolic reactions in cancer patients. Experimental tumors generally comprise 15%–30% of the host body weight at the time for metabolic experiments, while the tumor mass in man generally is less than 5% of body weight. The metabolic rate in mice and rats, which are the most frequent experimental animals, is ten times higher than in man. These factors and other species characteristics may be of importance for both quantitative and qualitative differences in the metabolic host reactions between experimental cancer and human cancer. Tumor-bearing animals usually do not show an increased total energy expenditure (1,2), but in human cancer, several reports have suggested an increased expenditure (3,4). The explanation for incongruent results of this kind may be that small animal decreases its normally high physical activity to save energy for the tumor demand.

The daily energy production in man at the cancer age is closer to the resting metabolic rate, which means that a decrease of physical activity will affect the total energy expenditure only to a minor extent. The decreased physical activity in tumor-bearing animals will, within a short time, probably lead to an altered feeding behavior and to metabolic reactions in peripheral tissues, which is of importance for the imbalance of the host-energy homeostasis. With these limitations in mind, we have previously validated a

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methylcholanthrene-induced sarcoma (MCG101) on black inbred mice (C57BL/6J) as an experimental model for mechanistic studies of cancer cachexia in man. We found that the alterations in glucose, lipid, and protein metabolism in the liver, kidney, and skeletal muscle tissue of these tumor-bearing animals were similar to those in cancer patients (5).

The metabolic characteristics of tumor cachexia may be the result of various paraneoplastic reactions, such as impaired nutrition and activation of the immune system of the host, or they may be mediated by more specific tumor factors. This discussion of tumor-host metabolism in peripheral tissues focuses on possible trigger mechanisms for this characteristic tumor-host metabolism.

GLUCOSE METABOLISM

Several studies have shown a normal or impaired glucose tolerance in combination with increased levels of fasting plasma glucose and altered insulin response to an oral iv glucose challenge in cancer patients (6,7). Tumor-bearing animals generally show lowered plasma glucose values (8), suggesting that the availability of glucose is insufficient to support both the host and the tumor.

Usually, these animals have decreased levels of circulating insulin, which has been explained as a result of the decreased plasma glucose. Cancer patients have essentially normal fasting plasma insulin, despite significantly increased levels of plasma glucose. The sum of insulin during an iv glucose challenge was significantly lower than in controls, suggesting that the sensitivity to glucose in the pancreatic β-cells may be decreased (7). In tumor-bearing animals there is evidence for hepatic insulin resistance as judged from the inability to build up their glycogen stores in response to exogenous insulin (8). Based on our experience, this insulin unresponsiveness is consistent with the decreased activity of glycogen synthase in liver tissue from the tumor-bearing animals. Insulin metabolism and insulin responsiveness in peripheral tissues have not been studied in tumor-bearing animals. Cancer patients, however, seem to have decreased assimilation capacity of glucose and decreased insulin responsiveness in peripheral tissues (9). The plasma glucose response to an exogenous insulin load (0.1 U/kg body weight) is smaller in cancer patients than in controls (9). Studies in cancer patients in vivo have shown an increased glucose production rate from alanine (10), lactate (11,12) and glycerol (our unpublished observations and a decreased glucose uptake in peripheral tissues. There seems to be an impaired feedback control in the liver, since gluconeogenesis is not slowed down when the glucose pool expands.

In skeletal muscle from cancer patients, the activities of enzymes regulating glycogen turnover, glycolysis, and oxidative metabolism are decreased (5). The enzyme activities were significantly correlated to decreased incorporation rates of glucose carbon into glycogen, lactate, and carbon dioxide in isolated muscle fibers (13).

This lowered capacity of glucose metabolism in muscles is consistent with the decreased insulin sensitivity or responsiveness in the entire organism. The increment in the synthesis of glycogen in response to insulin was accordingly smaller in muscle tissue from cancer patients than from matched controls (9). However, insulin stimulation of the protein synthesis rate in muscle tissue did not differ between cancer patients and controls, suggesting that the insulin resistance of the glucose metabolism was due to factors beyond the receptor level. Insulin unresponsiveness and decreased enzyme activities in muscle tissue of the tumor host are consistent with the selective effect on muscle fiber types. We have studied the ultrastructural changes in musculus semitendinosus of our tumor-bearing mice (unpublished observations). In this muscle, the red, slow, and oxidative type I fibers constitute 15%, the white, fast, and oxidative type II A fibers constitute 50%, and the white, fast, and glycolytic type II B fibers constitute 35%. The total number of fibers was unchanged in the tumor host, but the fiber volume had decreased, mainly the type II fibers. Type I fibers accounted for 3%, type II A fibers for 34%, and type II B for 63% of the total decrease in muscle volume. The mitochondrial density volume decreased as well, and again mainly in type II A and type II B fibers. Thus these fibers accounted for more than 90% of the total decrease in mitochondrial volume. This selective response in muscles may be of great importance for glucose and fatty acid metabolism in the entire organism of the host.

TPN of cancer patients for about 15 days influenced neither their muscle enzyme activities nor the in vitro flux of glucose significantly, but it did cause an increase in the protein synthesis rate in the muscle tissue. These findings make it unlikely that the depressed glucose metabolism in the muscle tissue is due only to decreased caloric intake. It is more likely that other factors, such as low physical activity, selective atrophy of muscle fibers, changed hormonal balance, or perhaps humoral tumor factors are of greater importance.

LIPID METABOLISM

Total lipids of the tumor host decrease as the tumor grows. This loss, which is mainly neutral fat, cannot be caused by decreased caloric intake only. Pair-fed rats and mice do not lose as much fat as tumor-bearing animals. Furthermore, force-feeding a high fat diet to tumor-bearing animals reduces but does not prevent

the loss of carcass fat. Our sarcoma-bearing mice decrease their total lipid content, while strictly pair-fed controls maintained their lipid stores and lean body mass (fig 1). In contrast to the tumor animals, the pair-fed controls thus were able to adapt to the decreasing energy intake, probably by changing their maintenance energy requirement.

Depletion of body fat is not always as obvious in human cancer patients. Recently, we found in an unselected group of cancer patients that many of them, even some with advanced cancer, had fat stores of the same size as in healthy controls (3). The mechanism underlying the fat loss in cancer patients and tumor-bearing animals is not known. Reasonably, it should be an imbalance between lipid synthesis and lipolysis in the adipose tissue. Insulin deficiency or insulin resistance in adipose tissue are factors favoring decreased lipid synthesis and increased lipolysis. Available data seem to indicate that there is a normal insulin sensitivity in adipose tissue of cancer patients and tumor-bearing animals. The inhibition of lipolysis in response to a glucose challenge, and the decrease in plasma free fatty acids after iv administration of insulin, were normal (14,15), as was the density of insulin receptors in lymphocytes from cancer patients (15). A relative deficiency of insulin may be one reason for the depletion of fat tissue in the tumor host. This is supported by the fact that insulin, to some extent, reduced the loss of fat in tumor-bearing animals (16).

The glycerol released during lipolysis is primarily metabolized in the liver, along different metabolic pathways. It functions as a substrate in the increased gluconeogenesis and can be oxidized or utilized in the synthesis of triglycerides and phospholipids. The distribution of the increased glycerol flux between these pathways in the tumor host is not known. The free fatty acids can also be metabolized along different pathways. It has been reported that only 1% of the rapidly turned-over free fatty acid pool is taken up by the tumor (17). Hyperlipidemia is common in experimental cancer but is not a prominent feature in cancer patients. Ketosis or ketonuria is not a frequent finding in cancer, so it seems probable that the fatty acids are oxidized, either directly or after being incorporated into hepatic glycerolipids and excreted as lipoproteins. The degree of hyperlipidemia may be a question of the capacity of muscles to oxidize fatty acids, which in turn depends on the muscle fiber type distribution, and of the availability of lipoproteinlipase activity. If this holds true, it is reasonable to find species differences concerning hyperlipidemia in tumor hosts.

PROTEIN METABOLISM

Protein metabolism in skeletal muscle is regulated by the supply of amino acids, hormones, and energy-generating precursors, as well as by physical activity. The time course of depletion of the skeletal muscle system in tumor hosts has not been assessed in terms of the relative importance of decreased protein synthesis as opposed to increased protein degradation. Both mechanisms probably operate in advanced cancer (18,19). It is unclear whether the catabolism of the skeletal muscles is produced by local factors in the muscles or by an increased drainage of substrates, as energy precursors and three-carbon intermediates to other organs and the tumor.

The caloric intake and the dietary components are modulators of the protein balance in skeletal muscles. A large body of information is available in translational modifications during protein-calorie malnutrition, but transcriptional events are probably also involved in the changed muscle protein metabolism of tumor hosts. We have previously described decreased incorporation rates of amino acids into acid precipitable muscle proteins in cancer patients in whom the caloric intake was probably decreased (18). Incubated isolated muscle fibers from the rectus abdominus muscle were used in these studies. Isolated muscle fibers synthesize peptides at a constant rate for a least 4 hours, and results indicating that the translational apparatus initiates in vitro reading of m-RNA have been published (20). The gradient of intracellular/extracellular potassium is essentially maintained during incubation and the protein balance in this preparation is sensitive to insulin, amino acids, and ions. The difference in muscle protein synthesis between cancer patients and controls was greatest when the incorporation rate of amino acids was maximally stimulated by high concentrations of amino acids in the incubation medium (18), which suggests that the decreased synthesis was a true decline in the synthesizing capacity. The incorporation rate of leucine into proteins was positively correlated to the RNA content of the muscle tissue.

The rate of protein synthesis and the RNA content in muscles from cancer patients could be significantly increased by TPN of the patient for about 15 days (fig 1). These findings are consistent with recent results in studies of tumor-bearing mice and pair-fed controls, implying that the reduction of food intake in the tumor mice is sufficient to decrease the muscle RNA content. However, decreased muscle protein synthesis in the tumor mice cannot be ascribed entirely to the reduction of food intake. Other contributing factors must be operating. The spontaneously decreased physical activity of the tumor-bearing animals is one possible factor and specific or unspecific remote tumor reactions are others. To analyze the possible role of the activated immune system in the tumor host we have studied the effect of immune stimulation by ip injection of antigen from *Corynebacterium parvum*. The rationale of us-

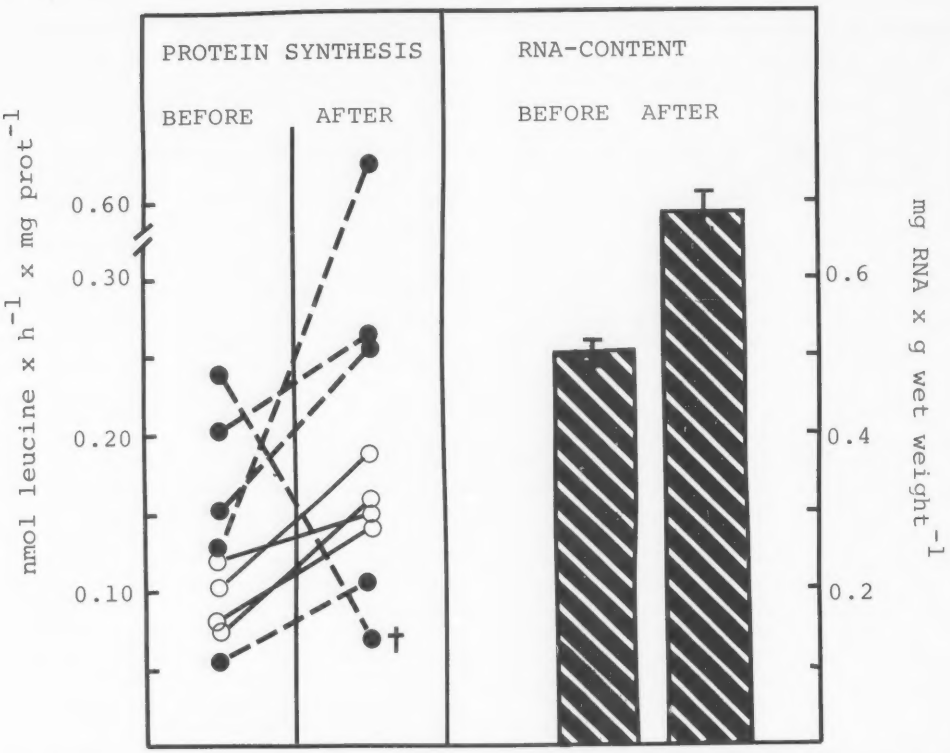

FIGURE 1.—Protein synthesis and RNA content in skeletal muscle tissue from cachectic patients before and after parenteral nutrition. Five patients with (●), and four patients without (○) cancer were given TPN for about 15 days with glucose, amino acids (Vamin^{R}) and lipids (Intralipid^{R}). They received 40–50 kcal/kg body weight. The nutrition contained 200 kcal/g N. The synthesis rates of proteins and RNA content were measured in vitro in incubated muscle fibers from the rectus abdominus muscle.

ing this model has been described previously (21). In our experimental animals (black inbred mice, C57BL/6J, these antigens cause the same histological changes in the spleen as the tumor growth. However, no specific effects on muscle protein synthesis by this stimulation were found.

According to Clark and Goodlad (22), the decreased protein synthesis in skeletal muscles from Walker tumor-bearing rats is due to a translational defect in the 40S ribosomal subunit. If this in vitro finding has any bearing on the in vivo situation, it could be expected that the synthesis of structural proteins and different sarcoplasmic proteins should be equally depressed, unless specific ribosomes for synthesis of specific proteins exist. There is no information suggesting such a differentiation in the translational apparatus. To examine if the synthesis of sarcoplasmic proteins was affected differently in the tumor-host, we labeled muscle proteins by ip injection of ^{14}C-leucine in our tumor-bearing mice, in starved mice (3 days), and in control mice fed ad libitum. Sarcoplasmic proteins were extracted and separated by ion exchange chromatography. The eluted protein fractions were subjected to analytical electrofocusing in polyacrylamide gels at pH 3.5–9.5. The significantly decreased synthesis was essentially confined to basic protein fractions as judged from the incorporated label. The synthesis of acidic proteins was largely unaffected. Similar results were obtained in cancer and starvation. These findings indicate differential changes of protein synthesis in skeletal muscles in cancer and starvation on sarcoplasmic proteins, and thus argue against the mechanism proposed by Clark and Goodlad. The underlying mechanism for this differential response is not known. Generally, acidic proteins have a more rapid turnover than basic proteins (23). However, if the precursor pools of amino acids for the synthesis of rapidly and slowly turned-over proteins are different, then we cannot exclude the possibility that the results may be due to isotope dilution.

This would, however, presuppose unevenly expanded or shrunken precursor pools of amino acids in tumor-bearing and starved animals. The lysosomal and proteolytic enzyme cathepsin D is probably involved in protein degradation in skeletal muscle tissue (18,24). Cancer patients and tumor-bearing animals have increased activity of this enzyme in skeletal muscle tissue (5). The increased activity of cathepsin D was significantly correlated to the fractional degradation rate of muscle proteins in vitro in cancer patients. The coupling between this enzyme activity in muscles and cancer was supported by the results of repeated measurements during progression of the disease and after curative surgical treatment (25). The enzyme activity was normalized after curative treatment and it increased further in patients with progression of the disease. According to our mice studies, the increased cathepsin D activity in muscle tissue was not dependent on decreased food intake. Pair-fed and starved mice did not show increased activity of the enzyme in muscle tissue. However, immune stimulation of mice by ip injection of *C parvum* antigens caused an activation of cathepsin D in muscles to the same level as found in the tumor-bearing animals. The role of the immune reactions in the tumor host for the increased activity of cathepsin D in muscles is not clear.

CONCLUSION

The presence of a malignant tumor causes a pronounced catabolic drive in peripheral tissues of the host. The decreased caloric intake of the host because of anorexia cannot alone explain this drive, but it is an important amplifying factor. The mechanisms of the remote effects of malignant tumors on host tissues are not fully understood. This area presents a challenge not only to our understanding of cell metabolism and metabolic interorgan relationships, but also to our knowledge of treatment of cancer patients.

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Summary of Discussions on the Host-Tumor Metabolism Session of the Conference on Nutrition of the Cancer Patient,

Daniel L. Kisner[1,*]

The discussion was opened by Dr. Kisner who briefly summarized the metabolic disturbances described by the four speakers. These included carbohydrate intolerance; decreased insulin responsiveness; increased glucose turnover and Cori cycle activity; increased gluconeogenesis from glycerol, alanine, and lactate; depressed glycogen synthesis; depressed peripheral muscle protein synthesis with increased catabolism; poorly regulated oxidation of amino acids; and an increased use of fatty acids as an energy source. Dr. Kisner then made the point that increased Cori cycle activity may be placing a significant energy drain upon the cancer patient. Energy realized by glycolytic metabolism of glucose takes place at least partially in the tumor, thereby depriving the patient of some undetermined fraction of this energy. Resynthesis of lactate to glucose not only requires energy for the process of gluconeogenesis, but also deprives the patient of high energy phosphates form oxidative metabolism. Thus the overall impact of accelerated Cori cycle activity is not precisely known, but may be quite significant.

Dr. Kisner then asked whether the accelerated gluconeogenesis (from whatever substrate) could be entirely secondary to malnutrition itself, rather than being directly caused by the tumor, in light of recent data that show that either TPN or simple glucose infusions appropriately suppress the process. Dr. Holroyde responded that he felt there was relatively little reason to believe that increased glucose turnover or Cori cycle activity was simply the result of malnutrition. He viewed increased glucose utilization as a requirement of cancer patients possibly as a compensatory mechanism for increased glucose demand made by the tumor itself. In support of this, he pointed to studies of tumor-associated hypoglycemia where glucose synthesis from lactate appears to be inhibited. Additionally, he pointed out that inhibition of gluconeogenesis with 3-mercaptopicolinic acid experimentally produces hypoglycemia in tumor-bearing animals. Dr. Brennan confirmed the occurrence of hypoglycemia in animals given 3-mercaptopicolinic acid and pointed out that tumor-bearing animals treated in this manner suffered more severe hypoglycemia and mortality compared to tumor-free controls. He concluded that it seems likely that the tumor-bearing animal is more dependent upon glucose as an energy source, possibly because of tumor glucose utilization.

Dr. Waterhouse commented that she did not believe that increased gluconeogenesis from alanine was entirely due to malnutrition. However, she added that studies that might demonstrate this definitively have not been done.Dr. Brennan agreed, but added that the degree of alanine conversion to glucose appears to correlate directly to the weight loss, regardless of whether it was tumor-induced or starvation-induced. This apparently holds true until the tumor burden becomes very large and the degree of alanine conversion to glucose appears somewhat higher than could be explained by malnutrition alone.

Dr. Kisner than asked the panel about the advisability of biochemically interrupting gluconeogenesis as a potential therapuetic maneuver for the cancer patient losing weight. Dr. Holroyde commented that this therapeutic step would make a great deal of sense if we could then provide the host with some energy-producing substrate not metabolized by the tumor. Barring that possibility, one might run the risk of hypoglycemia and even lactic acidemia.

From the audience, Dr. Joseph Gold commented on his experience with the gluconeogenesis inhibitor, hydrazine sulfate. He stated that hydrazine has been used in thousands of cancer patients without serious ill effects, and that anecdotal reports of appetite increase and weight gain exist. Additionally, he commented on a study performed by Dr. Gershanovich in the USSR which indicated a 60% subjective improvement rate in patients treated with hydrazine sulfate. Subjective effects included euphoria, increased activity, and pain relief, among others. Dr. Gold provided no specific data from this study with regards to appetite improvement or weight gain.

Dr. Kisner then commented that he found the obvious fat-wasting seen in cancer patients somewhat curious in light of considerable evidence that these patients have normal control mechanisms for lipolysis intact. He presented the hypothesis that fat-wasting oc-

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curred largely during periods of intermittent fasting when the cancer patient's insulin levels were low. He added the suggestion that increased utilization of fatty acids as an energy source during fasting might be due to depressed glycogen stores rendering the cancer patient relatively intolerant of even short fasts. In support of this, he pointed to the demonstration of decreased glycogen synthesis in the peripheral skeletal muscles of patients, demonstrated by Dr. Lundholm and his group. Dr. Lundholm then commented that he felt this was indeed a good possibility, but added that there were no data available relating to hepatic glycogen synthesis in cancer patients.

Dr. Kisner ended the discussion with the comment that virtually all of the metabolic disturbances discussed in the session would tend to leave the cancer patient unable to compensate normally for periods of intermittent fasting, obliging him to utilize amino acids and fatty acids as energy sources during these periods. He suggested that one potentially productive avenue for future research might be the investigation of glycogen synthesis in the cancer patient and the consideration of possible therapeutic means of increasing glycogen synthesis during periods of food intake. As one possibility, he suggested the study of the therapeutic use of insulin during periods of feeding.

The Impact of Malnutrition on Treatment Results in Breast Cancer

William D. DeWys,* Colin Begg, Pierre Band, and Douglas Tormey[1]

In a previous publication, we surveyed the effect of prechemotherapy weight loss on prognosis and response to chemotherapy in 11 different tumor types, using data from the Eastern Cooperative Oncology Group (1). The frequency of weight loss ranged from 31% for favorable non-Hodgkin's lymphoma to 87% for gastric cancer. Survival was shorter for patients with weight loss in all tumor types except acute leukemia and gastric and pancreatic cancer. Chemotherapy response rates were lower in patients with weight loss, but only for breast cancer was this difference statistically significant.

In this paper we focus on breast cancer as a prototype to illustrate the impact of malnutrition as measured by weight loss on the results of chemotherapy. Because performance status and tumor extent would also be expected to affect treatment results, we have analyzed the interactions of these variables and weight loss on treatment outcome.

MATERIALS AND METHODS

Data included in this analysis are derived from case records of patients participating in protocol 2173 of the Eastern Cooperative Oncology Group. All patients had histologic confirmation of malignancy and had received no previous chemotherapy. At the time of entry into this protocol, patients had disease extent judged to be beyond the scope of curative surgery or radiation therapy.

Pretreatment data were recorded on disease-specific on-study forms, and these data were entered into a central computer file. Pretreatment data included degree of weight loss during the 6 months prior to chemotherapy. Weight loss information was collected by patient interview, expressed as a percent loss compared to the patient's pre-illness weight, and was divided into the following categories: none, 0%–5% of body weight, 5%–10% body weight, and >10% body weight. Activity level or performance status was scored using standard Eastern Cooperative Oncology Group criteria:

0—fully active;
1—ambulatory, capable of light work;
2—in bed < 50% of time, capable of self-care but not of work activities;
3—in bed > 50% of time, capable of only limited self-care;
4—completely bedridden.

Patients who on review did not meet the eligibility criteria for this protocol and for whom weight loss data were unavailable were excluded from this analysis.

Tumor involvement was coded as absent or present for three specific anatomic sites: liver, lung, and bone. This tumor score cannot be equated with total tumor volume, since organ involvement below the level of clinical detection will be scored zero and involvement of organs of differing severity will be weighted equally.

Tumor regression after chemotherapy was graded using standard criteria. A complete response (CR) was defined as complete clearing of all evidence of tumor recalcification of osteolytic bone lesions. A partial response (PR) was defined as a >50% decrease in the cross-sectional area of measurable tumor and/or partial recalcification of osteolytic lesions. Patients were randomly assigned to receive doxorubicin and vincristine; cyclophosphamide, 5-FU, and methotrexate; or cyclophosphamide, 5-FU, methotrexate, and prednisone. Although differences in response and survival related to assigned treatment were observed (2,3), these differences were small enough to permit pooling of data for the present analysis. Frequency distributions were tested for significance using the Chi-square test of association. Survival data were subjected to significance testing using the log-rank test for survival distribution (4). Survival medians were calculated using the method of Kaplan and Meier (5).

When the prognostic effect of weight loss was analyzed in reference to another prognostic factor, a method for the analysis of several 2 x 2 contingency tables was applied (6). This provides a single statistical test of the effect of weight loss after adjusting for the prognostic effect of the other variables.

[1]This study was conducted by the Eastern Cooperative Oncology Group (*Paul P. Carbone, chairman*, CA-2115) and was supported by Public Health Service grants (CA) from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. The following members participated in the formulation and analysis of this study: National Cancer Institute, Bethesda, MD (*W. D. DeWys*); Harvard University, Boston, MA (*C. Begg*, CA-23318); Institut du Cancer de Montreal Notre Dame Hospital, Canada (*P. Band*, CA-21653); and Wisconsin Clinical Cancer Center, Madison, WI (*D. Tormey*, CA-2115).

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Incidence of Weight Loss

The frequency of weight loss is presented in table 1. Although many clinicians regard cachexia as a minor problem in breast cancer, 36% of patients had noted weight loss prior to chemotherapy and 6% had lost >10% of their body weight.

TABLE 1.—Frequency of weight loss prior to chemotherapy for breast cancer

Weight loss category	Number of patients	%
None	210	64
0%-5%	75	22
5%-10%	27	8
> 10%	18	6
Totals	320	100

Prognostic Effect of Weight Loss

The correlation between weight loss and survival is presented in table 2. Patients having any degree of weight loss had a median survival that was less than two thirds that of patients who had not lost weight. Increasing degrees of weight loss had little effect on further shortening of survival, in contrast to data for most tumor types which show that survival tends to decrease with increasing degrees of weight loss (1).

The correlation between weight loss and response to chemotherapy is presented in table 3. Patients with pretreatment weight loss had a lower overall response rate. Most of the difference was attributable to differences in CR rate. CR was 2½ times more frequent in patients without weight loss compared to patients with weight loss.

TABLE 2.—Effect of weight loss on median survival in breast cancer

Weight loss category	Median survival each category	Median survival (wks) combined
None	69	69
0%-5%	46	
5%-10%	41	45*
> 10%	43	
(P value)†	0.02	< 0.01

*All categories of weight loss (0%-5%, 5%-10%, and > 10%) have been combined.

†The *P* values refer to a test of the hypothesis that the entire survival curves are identical, not merely a test of the medians. However, the median is a representative indicator of the survival distribution, and consequently its use as a summary statistic is acceptable.

TABLE 3.—Effect of weight loss on response to chemotherapy for breast cancer

Weight loss	No. of patients with response/no. treated		
	CR	PR	CR+PR
No	37/210 (18%)	91/210 (43%)	128/210 (61%)
Yes	8/120 (7%)	44/120 (37%)	52/120 (43%)
(*P* value)	(P=0.01)	NS*	(P=0..01)

*Not significant.

Interrelations Between Performance Status and Weight Loss

The interrelationship between performance status and weight loss is shown in table 4. The majority of patients who were ambulatory had not lost weight while a majority of those with some limitation of activity had experienced weight loss.

The interaction between performance status, weight loss, and median survival is indicated in table 5. Among active and ambulatory patients, weight loss correlated with a signficantly shorter survival. For nonambulatory patients, however, there was no correlation between weight loss and survival. These data are representative of data from all tumor types (1). In 7 of 11 tumor types, survival was shorter with weight loss in favorable performance strata while within the unfavorable performance strata survival was shorter with weight loss in only one tumor type.

The effect of prior weight loss and performance status on response to chemotherapy is similar to that for survival (table 6). Weight loss correlated with reduced response rate within the favorable performance strata. When CR was analyzed separately, weight loss was associated with a lower CR rate which was statistically significant when analyzed by the method for several 2 x 2 contingency tables (table 7) (6).

Interrelationship Between Tumor Extent and Weight Loss

The frequency of weight loss increased with increasing number of visceral organs involved with metastases. Patients with two or more visceral sites involved were nearly twice as likely to have lost weight than patients free of visceral metastases (table 8). A similar trend was found only for sarcoma and colon cancer in our survey of different tumor types and only in breast cancer was this correlation statistically significant (1).

The interaction between disease extent, weight loss and median survival is presented in table 9. Within each stratum of disease extent, weight loss was associated with a median survival shorter than that of patients without weight loss. In our survey of tumor types, weight loss exerted a prognostic effect in pa-

TABLE 4.—Relationship between weight loss and performance status*

Performance status	Total no. patients	No. of patients with weight loss			
		None	< 5%	5%-10%	> 10%
0	113	99 (88%)	11 (10%)	2 (2%)	1 (1%)
1	123	74 (60%)	32 (26%)	10 (8%)	7 (6%)
2	66	32 (48%)	22 (33%)	9 (14%)	3 (5%)
3	28	5 (18%)	10 (36%)	6 (21%)	7 (25%)
Totals	330	210 (64%)	75 (23%)	27 (8%)	18 (5%)

*$P < 0.001$.

TABLE 5.—Effect of prior weight loss and performance status on median survival

Performance status	Median survival (wks)		
	No weight loss	Weight loss	*P* value
0-1	77	56	< 0.02
2-3	37	37	NS*
Totals	69	45	< 0.01

*Not significant

TABLE 6.—Effect of prior weight loss and performance status on response to chemotherapy

Performance status	Response rate (CR+PR)		
	No weight loss	Weight loss	*P* value
0-1	113/173 (65%)	31/63 (49%)	0.03
2-3	15/37 (41%)	21/57 (37%)	NS*

*Not significant

TABLE 7.—Effect of prior weight loss and performance status on CR to chemotherapy*

Performance status	No. of CR/no. of patients treated	
	No weight loss	Weight loss
0-1	34/173 (20%)	6/63 (10%)
2-3	3/37 (8%)	2/57 (4%)

*$P = 0.05$, - Significance testing using the method for analysis of several 2 x 2 contingency tables (6).

TABLE 8.—Correlation between extent of disease and frequency of weight loss in breast cancer*

Visceral metastases (lung, liver, bone)	Frequency of weight loss (no. of patients with weight loss/no. studied)
≥ 0	22/83 (27%)
≥ 1	51/148 (35%)
≥ 2	47/99 (47%)
Totals	104/289 (36%)

*$P = 0.01$.

TABLE 9.—Effect of disease extent and weight loss on median survival in breast cancer

Visceral metastases	Median survival (wks)	
	No weight loss	Weight loss
0	88	62
1	66	55
2 or 3	58	40
Totals	69	45

tients with limited tumor extent in three tumor types, but in more advanced categories of tumor extent, weight loss did not adversely affect survival (1).

Analysis of the interaction of disease extent, weight loss, and response to chemotherapy in breast cancer shows a consistently lower response rate for patients with weight loss compared to those without weight loss within each tumor extent category (table 10). The effect of weight loss on response was approximately equal to the effect of tumor extent. Weight loss also affected the likelihood of a CR to chemotherapy within each tumor extent category (table 11).

TABLE 10.—Effect of disease extent and weight loss on overall response to chemotherapy in breast cancer*

	No. of responses (CR+PR) no. of patients treated	
Visceral metastases	No weight loss	Weight loss
0	40/61 (66%)	12/22 (55%)
1	59/97 (61%)	24/51 (47%)
≥2	29/52 (56%)	16/47 (34%)

*$P = 0.01$.

TABLE 11.—Effect of disease extent and weight loss on CR to chemotherapy in breast cancer*

	No. of CR no. of patients treated	
Visceral metastases	No weight loss	Weight loss
0	14/61 (23%)	4/22 (18%)
1	16/97 (16 %)	2/51 (4%)
≥2	7/52 (13%)	2/47 (4%)

*$P = 0.01$.

DISCUSSION

This analysis has delineated the prognostic effect of weight loss on response to chemotherapy and survival for patients with breast cancer.

Performance status and tumor extent are important prognostic factors, but the analyses presented display the independent contribution of weight loss on response to chemotherapy and survival for patients with breast cancer. Our conclusion is similar to that of a multivariate analysis of colon cancer patients, that weight loss is a powerful independent prognostic factor (7).

The correlation between weight loss and performance status suggests that the two may be interrelated or may have a common basis. Weight loss drawn from the muscle compartment may be expected to decrease a patient's performance status. Thus, for those patients whose weight loss correlates with a lower performance status, the weight loss was probably drawn proportionately from the muscle compartment. Weight loss without deterioration in performance status may reflect loss of fat stores with relative preservation of muscle energy stores. Deterioration of performance status without weight loss may reflect loss of muscle and increase in body fat or total body water. Increases in total body water with advanced cancer have been described (8). Deterioration of performance status without weight loss might also be related to other factors such as anemia, pain, etc. One mechanism by which weight loss could affect survival is muscle wasting and consequent increased susceptibility to pulmonary complications.

Differences in response to chemotherapy by weight loss status probably reflect the effect of weight loss on tumor cell kinetics. As host weight loss increases, the growth rate of a tumor slows down (9,10). A major determinant of this slowing of tumor growth rate is a diversion of tumor cells from a proliferating state to a nonproliferating state (11), which decreases their sensitivity to chemotherapy (12,13). This change in cell kinetics may explain differences in response rate related to weight loss status.

Clinicians have long recognized that large weight losses have adverse effects on the prognosis of cancer patients. For example, for Hodgkin's disease, weight loss of >10% of body weight in the previous 6 months places patients in the B category with an expected shorter survival (14,15). The present results are noteworthy in demonstrating that even small amounts of weight loss (<5% of body weight) may significantly worsen prognosis. Also noteworthy is our observation that the prognostic effect of weight loss was greatest in patients with other favorable prognostic factors, such as good performance status.

This analysis has relevance for the conduct of future trials of chemotherapy for cancer. In randomized trials stratification by weight loss should be considered to assure a balance of this prognostic factor between treatment groups. In studies with historical controls, the weight loss status of both groups should be known to test the validity of their use.

These observations are also relevant for planning trials of nutritional intervention in cancer patients. Nutritional supportive therapy should be studied as a means of improving prognosis. Differences in tumor response rates and survival should be evaluated as endpoints for assessing the value of nutritional intervention. The tumor type should have a moderately good response to chemotherapy and a moderately good survival to maximize the chance of improvement with nutritional intervention. Also, since performance status strongly affects prognosis, the intervention could include efforts such as physical therapy to improve performance levels. A trial of this type is currently being supported by the Diet, Nutrition, and Cancer Program of the National Cancer Institute for patients with small-cell lung cancer.

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Effect of Total Parenteral Nutrition on Tumor-Host Responses in Rats[1]

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SUMMARY

Total parenteral nutrition (TPN) is a clinical adjunct to cancer therapy. But it is difficult to do controlled clinical studies on cancer patients undergoing TPN. We therefore turned to a study of TPN on Buffalo strain rats with and without a Morris 7777 transplantable hepatoma. Our results showed that TPN at higher than normal levels (total parenteral hyperalimentation, abbreviated TPH) supported a gain in body weight of nontumorous rats. In tumorous rats, TPH supported body weight gain and stimulated tumor growth. Detailed analysis showed the TPH of the rats with a large rapidly growing hepatoma did gain body weight associated with fluid retention while the carcass weight decreased. Nor did TPH of tumorous rats significantly reverse the low cell proliferative activity to ear epidermis attributed to the tumor though it did stimulate tumor cell proliferation. Thus TPH by itself did not overcome wasting due to presence of the tumor. Using the hypothesis that uncontrolled gluconeogenesis is linked to cancer cachexia, we combined TPH with inhibition of gluconeogenesis (using hydrazine sulfate) and prevented the carcass weight loss (cachexia) in the tumorous rats. Tumor growth was stimulated by this treatment. Stimulation of cell proliferation in the tumor can, however, benefit chemotherapy using an S phase or cell cycle-specific cytotoxic drug.

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The advent of total parenteral feeding procedures for rats by Steiger et al in 1972 (1) gave the unique opportunity to test how controlled hyperalimentation would influence cell proliferation and other parameters in the tumor and in the host. Another reason for this experimental work is that total parenteral nutrition has been reported to be of value to cancer patients who are undergoing therapy (2–6). It is difficult to do controlled studies on cancer patients undergoing total parenteral feeding because of numerous variables. Therefore, we turned our attention to the study of total parenteral hyperalimentation (TPH) on Buffalo (BUF) strain rats bearing a transplantable nonmetastasizing Morris hepatoma (No. 7777).

Specifically we reasoned that forced feeding (hyperalimentation) of animals with rapidly growing tumors would increase the systemic levels of nutrients in the host, causing: (*a*) augmented stimulation to those cell populations which were specifically and strongly stimulated by tumor product (ie, endothelial cells of blood vessels, sinusoidal lining, and Kupffer cells in the liver as well as leukocytes); and (*b*) would perhaps permit renewing cell populations, which were not stimulated by the tumor products, to increase cell proliferation to normal levels (ie, ear epidermis and the ventral tongue epithelium) (7). We also questioned how tumor growth and cell proliferation activity would be influenced by such hyperalimentation.

MATERIALS AND METHODS

Because the materials and methods for parenteral hyperalimentation have been given in detail elsewhere (1,6,8), only a brief description will be given here. The parenterally fed rats had a silastic catheter tube inserted into the superior vena cava or the right atrium via the external jugular vein. The other end of the catheter existed the body between the scapulae. The rat was placed in a padded harness and attached to the fluid infusion swivel apparatus (Instec Labs, Philadel-

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phia, PA) via a tightly wound steel shielding cable, housing the plastic infusion tubing. These harnessed rats were housed individually in metabolic cages during the study and were infused by a model 903 Holter pump. A 27% solution of glucose and 3.9% solution of Freamine (McGaw Laboratories) with electrolytes and multivitamins were infused (9). The detailed formula of this elemental diet is listed by Cameron et al (9). These rats were fed 13 k cal/100 g body weight the first day of infusion, 20 k cal/100 g on the second, and 26 k cal/100 g from Day three until the end of the experiment.

Sixty-one young male BUF strain rats were used in this study. Half of the rats were inoculated sc in the flank with a suspension of Morris hepatoma 7777 cells (8). All rats were then placed in metabolic cages. Body weight and tumor size were recorded regularly. Three weeks after tumor inoculation the rats were placed on the feeding regimen to which they were randomly and previously assigned. Information on the feeding and tumor conditions for each experimental group is summarized in tables 3 and 4. All rats were harnessed for the duration of the experiment. Rats in the solid food groups were given Lab Blox (Wayne, Allied Mills, Chicago) and water ad lib. The remaining rats were given liquid diets either po ad lib., or iv.

All animals in the experiment (except those killed as the "zero-time" control groups) were anesthetized with ether and fitted with a harness at the time the various feeding treatments were started (ie, 3 weeks after tumor inoculation). Two groups of rats on solid food po (one with and the other without a tumor) were killed by ether overdose at the start of the feeding procedure (zero-time control groups). All other rats were sacrificed 1 week after the start of the various feeding treatments. The tips of the indwelling iv catheters were removed at the time of sacrifice and cultured for up to a week at 37 °C on nutrient agar Petri dishes. There was no visible growth of microorganisms from the catheters.

One hour before sacrifice each rat was given an ip injection of tritiated thymidine (6 Ci/mM) at a dosage of 1 Ci/g body weight in 0.9% NaCl solution. Samples of ear, tumor, and ileum were fixed in 3% paraformaldehyde for histology and radioautography (10). The histological radioautographic counting procedures were as follows: the ear was cross sectioned 1 cm from the tip and the percent of labeled cells in the basal layer in the entire epidermis was scored. More than 1000 cells were scored for each tissue in each rat. Cross sections of the lower ileum 1 cm from the ileocecal junction were taken for radioautography. The number of labeled cells was counted in crypts that demonstrated an open lumen from the crypt-villus junction to the base of the crypt. This open lumen condition assures a reproducible counting situation. At least ten such crypts were counted for each rat. The radioautographic labeling index of the tumor was done with the microscope by placing the center line of an ocular grid parallel to a vessel and then scoring all labeled and unlabeled hepatoma cells within 37 μ of this line. The need to restrict radioautographic analysis to 37 μ of a blood vessel is shown in the micrograph in figure 1, which shows that this is the area or zone of proliferative activity in the tumor (at least 1000 cells were scored for each tumor).

Data from the different experimental groups were subjected to one-way analysis of variance (ANOVA). When a significant ANOVA was found, the significant differences of the various mean values were determined by calculating the critical difference between means according to Bruning and Kintz (11).

RESULTS

TPH in Rats With and in Rats Without the Tumor

Before presenting the results on cell proliferation it is important to briefly review some key background results from earlier reports.

The data presented in table 1 are from a previous report, which showed that TPH supports growth of body weight of young nontumorous BUF rats over a 10-day period (12).

The data presented in table 2 are from another previous report, which showed that TPH of young tumorous BUF rats supported body weight gain and stimulated tumor growth (8).

The data presented in table 3 summarizes previously published data done on the rats described in the Methods and Materials section (9). The data in this table give a more complete analysis of effects of TPH on numerous tumor-host responses and serve to help understand the effects of a rather large and rapidly growing tumor in rats. The results of this study

TABLE 1.—Rate of body weight gain before and after start of TPH in 7 rats (mean ± SE)*

	Kcal intake/ 5 days	Slope of body weight growth/day†
Before TPH (ie, rats fed solid food ad lib.)	92 ± 6	0.0039 ± 0.0008
Rats changed to TPH for 10 days	120 ± 11	0.0227 ± 0.0012‡

*Data from Cameron et al (12).

†Natural log of grams which gave the best correlation to growth data.

‡Students t-test shows this value to be significantly increased over the value before TPH ($P < 0.01$).

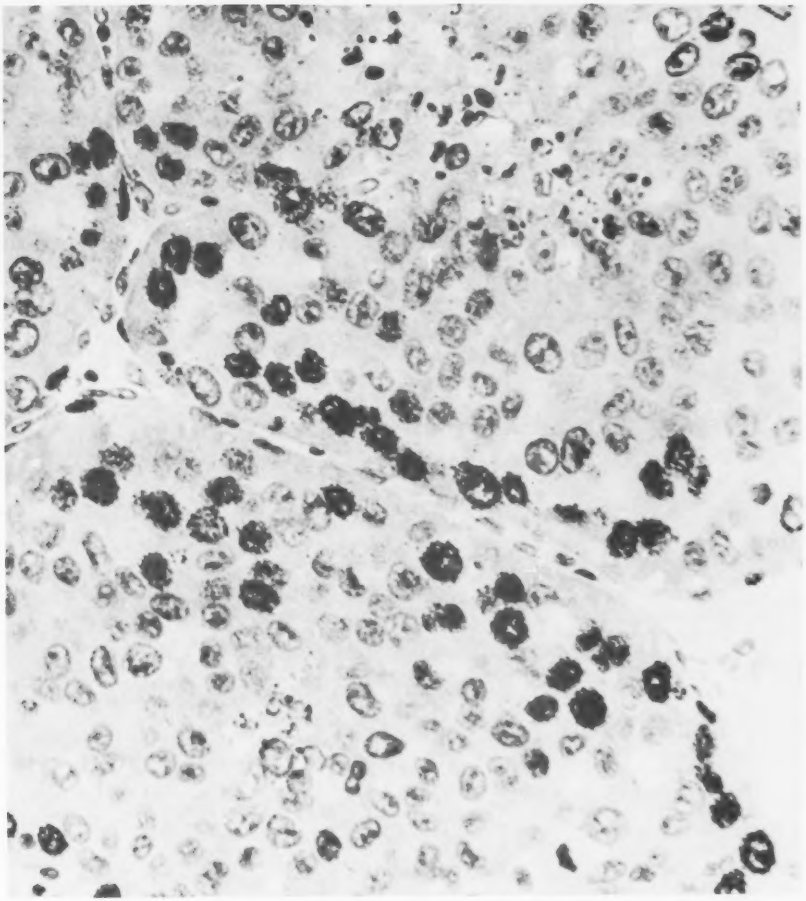

FIGURE 1.—Radioautograph of Morris hepatoma 7777 from a rat 4 weeks after sc tumor inoculation. The host BUF rat was fed on solid food for 1 week prior to receiving an ip injection of tritiated thymidine 1 hour before the rat was sacrificed. Cells with a labeled nucleus are positioned adjacent to the blood vessels while no labeled cells are near regions of necrosis (N). (H&E stain; x800).

showed that the presence of the large rapidly growing hepatoma was associated with higher mortality, fluid retention, a decrease in carcass weight, leucocytosis (including lymphocyte and all other cell types), anemia, and a decrease in serum IgG and transferrin. The iv feedings forced food intake well above the po ad lib feeding level inthe tumor-bearing rats. The degree of positive nitrogen balance was similar in nontumorous rats on the same liquid diet formula when given iv or po. The iv feeding of tumorous rats maintained the same degree of positive nitrogen balance but the po ad lib feeding resulted in a significantly lower nitrogen retention. The data indicated that the iv-fed tumorous rats retained fluid but lost carcass weight. Thus the rapidly growing tumor appeared to take priority over the maintenance of carcass mass even in the iv hyperalimented rats.

Tumor on Cell Proliferation in Host Tissues

The mean cell labeling index was consistently lower in the ear epidermis in rats with large tumors regardless of the feeding treatment (table 4). The presence of a large tumor was responsible for a significant decrease in the number of labeled cells per crypt in only one of the feeding treatment comparison groups (table 4), the

TABLE 2.—TPH on body weight and tumor weight*

Feeding treatment	Parameter measured	Start feeding treatment	1 week later	2 weeks later
Solid food po; ad lib. (9 rats)	Average kcal intake/wk		127	109
	Body wt (g)	224	243	248
	Tumor wt (g)	0.8 ± 0.1	2.4 ± 0.3	5.2 ± 1.0
Total parenteral feeding (14 rats)	Average kcal intake/wk		150	185
	Body wt (g)	224	223†	237
	Tumor wt (g)	0.8 ± 0.1	6.4 ± 1.2‡	11.6 ± 1.7‡

*Data from Cameron and Pavlat (8).

†The failure to gain weight during this first week of TPH may be due to the graded increase in calorie intake given over the first 3 days of iv infusion.

‡Significantly larger tumor compared to tumors in rats fed solid food po, ad lib.

TABLE 3.—Effect of parenteral nutrition on various tumor-host responses*

	Without tumor			With tumor		
	Solid food	Liquid food		Solid food	Liquid food	
	po	iv	po	po	iv	po
% Mortality during experiment	0	13	0	25	33	0
% Terminal carcass weight as % of body weight	81	84	86	73	71	75
Terminal water content of carcass (%)	63	62	62	65	65	64
Terminal leukocyte count (x 10^3/cm^{-3})	11	13	12	22	25	19
Terminal spleen weight (% of body weight)	0.23	0.28	0.23	0.20	0.39	0.38
Terminal hematocrit	49	48	49	29	27	34
Terminal serum transferrin (% of total protein)	10.4	8.5	10.3	5.9	5.1	4.9
Terminal serum IgG (% of standard IgG)	74	64	69	26	27	42
Metabolizable caloric intake in first 5 days/ 100 g body wt	97	120	102	30	123	75
Nitrogen balance, last 2 days (mg N in−mg N out/100 g body wt)	—	103	104	—	100	56
Fluid balance (fluid in/urine out/100 g body wt)	1.29	2.65	2.82	1.46	3.31	3.14

*From Cameron et al (9). No animals died during the first 5 days, thus nonterminal data include all rats and terminal data include those rats killed at termination (7 days).

group with the lowest food intake (ie, the rats on solid food po with large tumors that average 13% of the rat's body weight). Comparison of the "zero-time" groups of rats on solid food po with and without tumors showed that the tumor averaged only 3.5% of the rats' body weight and that the number of labeled cells per crypt was not significantly decreased in comparison to the group of rats without the tumor.

Various Feeding Treatments on Cell Proliferation in Rats With and in Rats Without the Tumor

The ear epidermis comparisons revealed no significant differences in the labeling index due to the various feeding treatments in rats without tumors (table 4). Notice, however, that the number of labeled cells per

TABLE 4.—Tumor size and cell proliferation activity of host tissues after 1 week of feeding treatment (mean ± SE) (radioautographic labeling index)*

Method of feeding and tumor condition	(n)	Tumor size % of body weight less tumor	Ear epidermis % labeled cells in basal layer	Tumor, % labeled cells within 37μ of blood vessel	Ileum, number of labeled cells per crypt
Solid food po†					
Without tumor	7	—	4.2 ± 0.4	—	23.4 ± 1.5
With tumor	8	3.5 ± 0.7	3.5 ± 0.1	54.7 ± 1.8	26.5 ± 1.4
Liquid food iv					
Without tumor	8	—	2.9 ± 0.5	—	15.6 ± 3.8
With tumor	3	14.1 ± 0.9	1.9 ± 0.2	54.5 ± 3.2	15.7 ± 0.9
Liquid food po					
Without tumor	7	—	3.3 ± 0.5	—	17.5 ± 0.9
With tumor	5	10.6 ± 2.8	2.3 ± 0.5	43.5 ± 1.9	18.4 ± 0.9
Solid food po					
Without tumor	5	—	3.4 ± 0.1	—	26.1 ± 1.8
With tumor	5	13.1 ± 1.8	1.2 ± 0.6	45.3 ± 2.9	21.8 ± 0.8
Statistical analysis‡					
F value		9.2	4.5	6.2	12.9
p value		< 0.001	< 0.001	< 0.001	< 0.001
Probability values					
< 0.05		5.3§	1.4§	7.4§	3.3§
< 0.01		7.3	1.8	10.0	4.4

*The rats were injected with tritiated thymidine 1 hour before sacrifice.

†These two groups of rats were killed at the time the other groups of rats were started on their specific feeding procedure. These two groups serve as "zero time" controls.

‡Data were subjected to a one-way analysis of variance test, then a multiple range test was used to determine significance of differences between means.

§Means in each column that differ by these values are significantly different at the indicated level of probability (p value).

intestinal crypt showed striking and significant differences which can be attributed to the method of feeding or to differences in the nutrient composition or to the nutrient level of the solid or liquid food. Rats given liquid elemental diet po and iv had a significantly lower number of labeled cells per crypt than rats on solid food po. The rats fed TPH had an even lower number of labeled cells per crypt than the rats fed liquid diet po.

The tumor normally showed healthy viable-appearing hepatoma cells arranged cylindrically around tumor blood vessels that project inward from the tumor capsule. Mitotic activity was highest near the axial blood vessel while necrotic regions occur as the distance from the blood vessel increased (fig 1). The central portion of the tumor often showed the collapse of an axial blood vessel with all surrounding cells undergoing necrosis. The central regions of the tumor contained larger areas of necrosis than regions closer to the tumor capsule which supplies the tumor's blood vessels.

The dynamic cell turnover of the Morris hepatoma 7777 used in this study is further appreciated by its high labeling indexes (table 4). A single pulse injection of tritiated thymidine labeled 44%–55% of the hepatoma cells within 37 μ of a blood vessel. Cell proliferation activity of the tumor also showed differences due to the different feeding procedures and to the size of the host's tumor mass (table 4). The rats on solid food with smaller tumors (zero-time control group) had a significantly higher tumor labeling index than the rats on solid food with larger tumors. Tumorous rats that were parenteral hyperalimented had significantly higher proliferative index in their tumors than tumorous rats fed liquid food po ad lib or tumorous rats on solid food po ad lib. TPH, therefore, significantly stimulated a higher tumor labeling index.

DISCUSSION

TPH on Tumor-Host Responses

Morgan and Cameron (7) proposed that a systemic reduction of nutritional precursors is caused by the needs of a rapidly growing hepatoma, which therefore accounts for a depression of cell proliferation and renewal in the tongue and the ear epithelium. The voluntary intake of food in the tumorous rats is demonstrated to be considerably lower (anorexia) than in the nontumorous rats (table 3). However, the forced feeding of tumorous rats at levels well above the tumorous rats fed ad lib (table 3) did not significantly reverse the decrease in cell proliferation in the ear. Apparently TPH of the rats with a large and rapidly growing hepatoma could not meet the nutritional demands of both the rapidly growing tumor and the host as reflected in loss of carcass weight in these rats. Thus, reduced nutritional levels or a metabolic derangement probably persist even in the TPH tumorous rats. Such a situation may account for the decreased cell proliferation in the ear.

The spleen weight and the leukocyte blood cell count are also elevated in the force-fed tumorous rats but not the force-fed nontumorous rats (table 3). Morgan and Cameron (7) have suggested that the increase in number of labeled leukocytes and the increase in spleen size is due to an attempt of the host to repel the foreign tissue of the transplanted hepatoma. The higher nutritional intake delivered by TPH enhanced the stimulated spleen size and leukocytosis to a significant extent (9).

An important finding is that TPH of tumorous rats stimulates cell proliferation activity of the tumor (table 4).

One finding relates to the feeding treatment rather than to the tumor presence. Specifically, the striking decrease in number of labeled cells per intestinal crypt which may be attributed either to (*a*) the lack of solid food (suggesting that the work load of digesting solid food may be an important factor in the control of cell proliferation in the intestinal crypts), or (*b*) to differences in nutrient content between solid and the elemental liquid diet formula (for further discussion, see ref 13).

Our studies show that the nutritional needs of the rapidly growing tumor take priority over the maintenance of carcass weight even during TPH (9). Likewise, cell proliferation activity of the ear epidermis was not maintained by the TPH of the tumorous rats, again suggesting that the rapidly growing tumor is taking priority for the nutrient elements present in the blood.

Past Observations on TPH Combined With Inhibition of Gluconeogenesis on Tumor Growth and Cancer Cachexia

Aware of our failure to prevent cancer cachexia in the tumorous rats by TPH alone, we have recently turned to an alternate approach to overcome cancer cachexia (14). Using the hypothesis that gluconeogenesis is a vital link in the process of cancer cachexia (15–17), we designed and executed an experiment to overcome cancer cachexia. We chose to keep blood amino acids and glucose levels high by TPH while simultaneously inhibiting gluconeogenesis by blocking phosphoenolpyruvate carboxykinase (PEP-CK) function using a well known inhibitor of gluconeogenesis, hydrazine sulfate (HS) (15). Using this hypothesis and this approach, we were able to prevent cancer cachexia in a controlled experimental situation, as shown from the data presented in table 5 (14). The prevention of cancer cachexia by the combination of TPH and use of an inhibitor of gluconeogenesis seems a significant advance. It is also possible that HS or other gluconeogenesis inhibitors spare carcass wasting by some undefined mechanism, other than inhibition of gluconeogenesis. The point is that HS has now been shown to prevent cancer cachexia in

TABLE 5.—Effect of hydrazine sulfate on body and carcass weight and tumor growth*

		Body and carcass weight data†			Tumor growth: slope of cross-sectional area (cm^2/day)		Nitrogen balance (mg N_2 in minus N_2 out/100 g body weight/24 hr)	
Feeding method	Drug treatment‡	Terminal body weight (g)	Body weight (% of initial)	Carcass weight (% of initial)	Before therapy	After therapy	Day 2 of treatment	Day 5 of treatment
iv	+ HS	410 ± 7.9	107 ± 0.8	84 ± 1.2	0.44 ± 0.01	0.81 ± 0.3	86.66	74.67
po ad lib.	+ HS	298 ± 8.3	88 ± 0.5	64 ± 0.7	0.62 ± 0.06	−0.20 ± 0.14	40.66	7.33
po ad lib.	none	342 ± 5.7	97 ± 0.6	76 ± 0.7	0.79 ± 0.07	0.81 ± 0.06	26.33	27.67

*Modified from Grubbs et al (14) with permission of the publishers, S. Karger-Basel.
†Initial body weight was not significantly different in the three groups of rats.
‡Hydrazine sulfate, 15 mg/kg, twice daily, ip.

combination with TPH, whereas TPH by itself did not prevent cancer cachexia in our tumor-host model system. The combined parenteral feeding plus the HS therapy sustained body and carcass weight with high nitrogen retention, but was associated with stimulation of tumor growth (table 5). We postulate that the systemic nutrient level was elevated by this combination therapy and that the cell proliferation activity in the ear epidermis was probably maintained at normal levels under such conditions, but we have not yet tested these predictions.

Prospects for Cancer Therapy Using a Combination of Hyperalimentation, Inhibition of Gluconeogenesis, and a Cell Cycle-Specific Cytotoxic Drug

Based on the toxic and carcinogenic nature of hydrazine sulfate (14,18), the drug itself would not seem to hold great promise as a cancer chemotherapeutic agent to overcome cancer cachexia in humans even when used with TPH. It is possible that some other known inhibitors of the PEP-CK reaction can be employed to inhibit gluconeogenesis. For example, pyridine-2,3-dihydrazide or L-tryptophan (19–21) might give the desired inhibition of gluconeogenesis without the harmful side effects. It has been shown that the stimulation of tumor growth can make a cell-cycle- or S-phase-specific cytotoxic drug, such as hydroxyurea, more effective (22). Thus the stimulation of tumor growth need not be without potential therapeutic benefit, as illustrated by enhanced tumor regression in one of our previous reports (22).

A most important implication of our research is that cancer cachexia can be overcome by inhibition of gluconeogenesis in combination with TPN at high nutrient and caloric levels. This finding adds credence to the concept that cancer cachexia involves a systemic energy-losing cycle dependent on an interplay of tumor glycolysis and gluconeogenesis (17).

We are currently planning a series of experiments to treat hepatoma-bearing rats by keeping blood amino acids and glucose levels high by TPH combined with inhibition of gluconeogenesis by high levels of L-tryptophan.

Thus TPH combined with inhibition of gluconeogenesis should stimulate cell proliferation in the tumor and inhibit cell proliferation in the small intestine. This situation may be beneficial when combined with cancer chemotherapy using an S-phase-specific cytotoxic drug. The rationale is that the tumor would be more susceptible to the S-phase cytotoxic drug while the intestinal cells are less susceptible. In any event, the TPH combined with inhibition of gluconeogenesis should maintain the host in a better nutritional state and temporarily bypass the need for a normal functional intestine.

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Enteral Versus Parenteral Nutritional Support in Cancer Patients

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SUMMARY

There are many theoretical and practical advantages to enteral rather than parenteral administration of nutrients. However, it is unlikely that enteral supplementation of nutritional intake as presently practiced will be successful as a primary therapy for most patients with the cancer cachexia syndrome. The most likely role of enteral nutritional support (ENS) is in conjunction with other therapies. This modality deserves evaluation in surgery with curative intent. Changes in diet are effective in reducing the gastorintestinal symptoms of abdominopelvic irradiation, but the effect of ENS on the hematologic toxicity of radiation therapy and on response rates and survival is unclear. Elemental diets can reduce the gastrointestinal toxicity of conventional doses of 5-FU, but they worsen the mortality and hematologic toxicity of higher doses. Factors such as protein, fat, and carbohydrate sources, degree of hydrolysis of protein, lactose content, and timing of dietary manipulations are important in evaluating the response to ENS.

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ENTERAL VERSUS PARENTERAL NUTRITIONAL SUPPORT IN CANCER PATIENTS

The theoretical and practical advantages of enteral rather than parenteral administration of nutrients include simplicity, economy, decreased side effects, improved maintenance of the integrity of the small intestine, and an improved insulin response, which may be important in maintaining anabolism (1). Disadvantages of enteral nutritional support (ENS) peculiar to cancer, include tumor and treatment-induced nausea, vomiting and malabsorption, and marked anorexia often seen in these patients. Theoretical disadvantages of parenteral nutrition include possible pharmacologic activity of high levels of circulating amino acids and delivery of a large glucose load to tumor tissue. There are few direct comparisons of the two routes in cancer patients; therefore, this paper primarily reviews published work on the use of enteral nutritional supplements in cancer in an attempt to delineate its present status and establish areas where research is needed.

Enteral "forced feeding" has been infrequently used in cancer; most investigators have varied the type of food ingested rather than the amount. The nature of the protein source, especially its degree of hydrolysis or "elemental" nature, has received a great deal of attention. However, these preparations also differ in other respects, including carbohydrate and fat sources, lactose content, and osmolarity. Several studies indicate that these factors, as well as the timing of nutritional support, are also important determinants of response.

ENS AS PRIMARY THERAPY

Several lines of evidence suggest that ENS as presently practiced is unlikely to be successful as primary therapy in many patients with the cancer cachexia syndrome. The first derives from metabolic balance studies done in humans. This technique is based on the observation that certain elements are found in relatively fixed proportions in normal lean body mass. If an organism retains these elements in these ratios, it may be fairly assumed that normal lean body mass is being made; conversely, significant deviation from these ratios suggests that lean body mass is not being repleted and that the elements retained are being used for other purposes (2). Underweight cancer-free subjects hyperalimented by the central venous route retained nitrogen (N), phosphorous (P), potassium (K), sodium (Na), and chloride (Cl) in ratios of 1/0(N).08(P)/3.1(K)/3.5(Na)/2.7(Cl) (3). These ratios held over wide variations of N intake. Furthermore, when intake of

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one of these elements was stopped, retention of the others was markedly reduced or abolished.

Metabolic balance studies on human cancer patients fed by the enteral route have been performed, and in all of them these elements were retained in abnormal ratios. One study examined eight patients with solid tumors and one patient with monocytic leukemia (4). Tube feedings were used to deliver 2258–4702 calories per day. Metabolic balance studies revealed P retention that exceeded that predicted by N retention. Clinically, four of the patients were felt to have had acceleration of their disease. Our own studies (5) have compared metabolic balance data from nine cancer patients hyperalimented centrally (CHA) and six cancer patients hyperalimented enterally (ENS) with data from similarly treated malnourished controls (table 1). The controls retained these elements in ratios that did not differ significantly from normal; however, CHA patients retained significantly less P than controls, and ENS patients retained significantly less P, K, Na, and Cl than controls. N retention was similar in all groups. It was also noted that cancer patients retained significantly less magnesium (Mg) than controls when hyperalimented by either route. These differences were due to urinary rather than fecal losses. Finally, serum albumin increased significantly less in cancer patients than in noncancer controls. Thus, although cancer patients retain N in response to CHA or ENS, much of this N is not used for repletion of lean body mass or synthesis of albumin. Comparison of centrally versus enterally hyperalimented cancer patients revealed significant differences in element retention, indicating the importance of solution used and/or route of administration. There was no significant difference in these parameters when noncancer patients were examined. Although conclusions about the superiority of one route over the other cannot be drawn from this data, it is clear that the type of solution and the route of administration are important determinants of cancer patient's response to hyperalimentation.

The other evidence comes from animal studies. Tumor-bearing Sprague-Dawley rats fed via stomach tube gained more weight than similarly fed controls without tumors; however, postmortem examination revealed that this was predominantly tumor weight (6). In rats that were fed equicaloric ad lib diets with varying amounts of protein (casein) tumor growth rate was directly proportional to the amount of protein ingested (7). Although there is no direct evidence that this is true in humans, these and other animal studies indicate that in many tumor systems nutritional supplementation via the enteral route results primarily in increased tumor growth.

These findings should be balanced against the report that tumor-bearing rats fed 12% casein diets supplemented with methionine and guanidoacetic acid had a marked improvement in carcass weight gain relative to tumor weight gain when compared to rats fed 12% casein diets without supplementation. This supplement was also effective in decreasing urea excretion in rats with advanced tumors, which suggests some nitrogen-sparing effect (8). When essential amino acids were systematically deleted from the diet of force-fed, tumor-bearing rats, there were marked variations in changes in the final tumor weight and the final carcass weight depending on the amino acid deleted (9). These results suggest that alterations in the amino acid composition of the diet may lead to improved host responses without excessive stimulation of tumor growth. This is an area of active research interest.

TABLE 1.—Comparison of metabolic balance data of cancer (ca) and cancer-free (non-ca) patients hyperalimented enterally (ENS) and parenterally (CHA). Adapted from Reference 5.

Group	Type HA*	ΔN (gm)	ΔP (gm)	ΔK (meq)	ΔNa (meq)	ΔCl (meq)	ΔCa (gm)	ΔMg (meq)	ΔAlb (g/dl)
Non-cancer	ENS	5.3	0.33	15.2	20.1	13.2	0.17	10.1	0.3
		(1)†	(0.06)	(2.9)	(3.8)	(2.5)	(0.03)	(1.9)	
Cancer	ENS	4.8	0.07	−3.1	−3.4	−5.5	0.09	−2.7	0.0
		(1)	(0.01)	(−0.65)	(−0.71)	(−1.14)	(0.02)	(0.07)	
Cancer	CHA	5.1	0.13	18.7	19.5	12.6	−0.03	3.2	0.1
		(1)	(0.03)	(3.7)	(3.8)	(2.5)	(0.0)	(0.63)	
Non-cancer	CHA	4.6	0.27	18.9	23.4	17.7	0.06	11.9	0.5
		(1)	(0.06)	(4.1)	(5.1)	(3.9)	(0.01)	2.6)	
P values									
Ca vs non-ca	ENS	NS	< 0.08	< 0.01	< 0.01	< 0.01	NS	< 0.02	< 0.10
Ca vs non-ca	CHA	NS	< 0.08	NS	NS	NS	NS	< 0.01	< 0.05
CHA vs ENS ca		NS	< 0.05	< 0.05	< 0.05	< 0.05	NS	< 0.05	NS
CHA vs ENS, non-ca		NS	NS	NS	NS	NS	NS	NS	NS

*Abbreviations: Type HA = type of hyperalimentation; ENS = enteral hyperalimentation; CHA = parenteral hyperalimentation; NS = not significant ($P > 0.10$).

†Numbers in parentheses are ratios (*see* text).

One study has compared the parenteral administration of a liquid diet using crystalline amino acids as a protein source to administration of the same diet via a surgically placed stomach tube. The rats were observed for 7 days. Two of nine intragastrically fed nontumorous rats died, as compared to one of eight intravenously fed animals. However, five of six (83%) rats with the Morris hepatoma died when fed intragastrically as compared to two of six (33%) fed intravenously (10). These numbers are of course too small for definite conclusions; further studies are clearly needed.

Although ENS is unlikely to be successful as primary therapy for many patients with the cancer cachexia syndrome, it may be useful in patients whose weight loss is exacerbated by such complications as fistulae, short bowel, obstruction, and tumor or therapy-induced vomiting and malabsorption. There may also be patients who at different times in the course of their disease are able to utilize nutrients to benefit the host rather than the tumor. Longitudinal studies would be helpful in this area. However, it would appear that the main role of ENS is in support of other therapies.

SURGERY

There are no complete prospective randomized studies evaluating the role of hyperalimentation by any route in cancer surgery. Preliminary results in one study using perioperative hyperalimentation for patients undergoing surgery for gastrointestinal malignancy showed no improvement in complication rate or mortality (11). This important study is continuing (Fischer, J.E., personal communication). Given the acknowledged benefits of ENS in other forms of surgery this type of support deserves consideration. Results must be analyzed not only in terms of perioperative complications and mortality, but also in terms of long-term recurrence rates and survival. As discussed above, the tumor stimulation and the block to repletion of normal tissue would suggest that hyperalimentation is relatively contraindicated when palliative surgery is performed.

RADIATION THERAPY

The primary areas to be examined are the effects of enteral feedings on gastrointestinal and hematologic toxicity, and on response rates and survival.

Gastrointestinal Toxicity

Studies demonstrating the protective effect of enteral feedings on abdominally irradiated subjects are more concerned with the type of nutritional support than the amount. Rats without tumors that were fed an elemental diet (casein hydrolysate) survived higher doses of abdominal irradiation than similar rats fed rat chow (12). Both groups ate ad lib and consumed roughly equal calories. After exposure of a loop of intestine to 1000 rads, L-proline absorption returned to normal more rapidly in rats given elemental diets (Flexical ^{R}) than in controls given only rat chow (13). Eighteen adult cancer patients receiving abdominopelvic irradiation were alternately assigned to a regular diet or Flexical throughout the period of therapy. Again, caloric intake was similar in both groups, but six of nine control patients developed significant diarrhea as compared to one of nine on elemental feedings (14). Investigators at Stanford found that palatability problems prohibited a definitive conclusion about the effects of elemental diets in their patients (Donaldson S.S., personal communication). However, prophylactic use of a gluten-free, lactose-free, low residue diet in children undergoing abdominopelvic irradiation resulted in a decrease in the incidence of acute and chronic radiation enteritis to zero (15, and Lemerle, A., personal communication). The effect of this diet on morphologic changes in the bowel and on absorption has not been reported. It should be emphasized that this diet contains none of the commercially available defined formula diets. Thus either this diet, or elemental diets given ad lib, can decrease the gastrointestinal side effects of abdominopelvic irradiation. The mechanism and extent of this protective effect are unknown; however, one important factor appears to be the absence of lactose.

Hematologic Toxicity

Rats fed an ad lib elemental diet 7 days before and 30 days after exposure to 700 rads total body irradiation had significantly better survival than controls fed ad lib rat chow. It had been previously established that death in this situation was usually due to bone marrow suppression, and it was inferred that the prolonged survival was therefore due to marrow protection. However, no wbc counts were done, so the point cannot be taken as established (16). Interestingly, the improved survival was not seen in rats that were begun on the elemental diet on the day of irradiation rather than 7 days before the diet; these rats actually had decreased survival. When tritiated thymidine was injected into rats on ad lib elemental diets, incorporation into marrow cells was noted to be 164% of control (ad lib rat chow). This increased cellular proliferation was suggested as a possible mechanism for the protective effect.

In subsequent studies these same investigators varied the ratio of nonhydrolyzed to hydrolyzed protein in several defined diets and repeated the total body irradiation (17). Survival seemed to improve directly as the proportion of hydrolyzed protein increased. How-

ever, in other experiments with the same proportion of hydrolyzed protein but different proportions of long-chain and medium-chain triglycerides this protective effect was seen, suggesting that the nature of the fat source is also important. Again, wbc counts were not done, so a protective effect of these diets on the hematologic system has not been directly demonstrated. Finally, in human cancer patients receiving abdominopelvic irradiation (3900–4040 rads) there was no difference in change in total wbc count between patients receiving ad lib Flexical and patients receiving ad lib regular diets. There was, however, some protective effect in lymphocytes (14). Thus it is not at all clear that enteral nutrition with ad lib elemental diets provide any significant marrow protection. There are no studies using tube feedings to ensure an adequate caloric and protein intake; no studies on protection of patients receiving radiation therapy in other locations (eg, breast, head, and neck); and no studies examining the ability of enteral supplements to improve tolerance to chemotherapy given after radiation therapy. Such studies are clearly needed.

Response to Therapy

The effect of various enteral feedings on tumor response and survival is also unclear. Elson and Lamerton (18) innoculated the Walker carcinoma into albino rats and compared response rates to various radiation schemes in rats given diets containing 20% protein and others given equicaloric diets containing only 5% protein. With one fractionation scheme, but not with others, they were able to cure 14 of 15 rats on the high protein diet as compared to two of 15 on the low protein diet (18). However, it was subsequently pointed out that this effect might be due to the genetic disparity between transplanted tumor and host tumor in this system, with the improved cure rate due more to improved ability to reject the tumor as foreign tissue than to reject it as tumor per se. Indeed, subsequent studies using a syngeneic tumor in rats showed no difference in cure rates at different levels of protein intake, although rats fed a 26% casein diet lived significantly longer after radiation than rats on an 8% or 62% casein diet (19). This model more closely approximates a spontaneously arising neoplasm. Thus the ability of increased protein in the diet to improve the cure rate of radiation therapy in naturally occurring tumors is still open to question.

In humans, there is one prospective trial in which patients with locally advanced gastrointestinal cancer were randomized to receive either standard diet or standard diet plus 300 calories of a commercially available high-nitrogen elemental diet three times a day (20). Patients taking the supplements had a mean intake of 37 kcal/kg/day as compared to 20 kcal/kg/day in the control group. Nitrogen intake was 0.27 grams/kg/day in the supplemented group versus 0.12 grams/kg/day in the control group. Treatment was not completely standardized; patients received slightly different radiation therapy doses, and some also received chemotherapy. There was no significant difference in survival between the two groups. However, when patients who had lost more than 10% of their ideal weight were examined, with all tumor types combined, supplemented patients had an average survival of 14 months, as compared to 6 months for controls. Clearly, further study is needed to determine if this is a significant difference.

CHEMOTHERAPY

Gastrointestinal Toxicity

The role of enteral nutrition in the amelioration of chemotherapy-induced gastrointestinal toxicity is unclear. Bounous, et al (21) performed a careful histological study of the gastrointestinal tract of rats treated with toxic doses (150 mg ip) of 5-FU (21). Rats fed an ad lib elemental diet (hydrolyzed casein) had better preservation of bowel wall tone and of villous structure than rats fed ad lib rat chow or whole (unhydrolyzed) casein. These authors noted that 5-FU caused a marked decrease in the dipeptidase activity of the mucosal epithelial cells. The importance of these enzymes in protein digestion has been established. It was reasoned that the free amino acids of the hydrolyzed dietary preparations could be absorbed under these conditions whereas intact proteins could not. This increased absorption was felt to be important in the regeneration of injured epithelial cells. In a companion study, humans receiving conventional doses of 5-FU (12 mg/kg qd for 6-9 days) were alternately assigned to eat normal hospital food ad lib or a defined formula diet (based on casein hydrolysate as a protein source). Patients on the elemental diet actually consumed more calories per unit body weight than controls (27.1 vs 20.4 kcal/kg). Rectal biopsies done after 5-FU treatment were normal in all 11 patients on the elemental diet, but were normal in only one of eight control patients (22). Other animal studies using clinical doses of 5-FU (15 mg/kg qd for 9 days) showed no deaths in animals on ad lib elemental or standard diets. Protein utilization was improved by the use of hydrolyzed rather than intact protein (23). These were tumor-free rats, so no comment can be made about lean body mass gain relative to tumor weight gain.

Unfortunately, subsequent work has raised questions about the value of elemental diets in patients receiving 5-FU. In one study, Sprague-Dawley rats were acclimated to several commercially available diets varying in the extent of protein hydrolysis. They then received 5-FU 25 mg/kg sc for 6 consecutive days. Diarrhea, stomatitis, hypoalbuminemia, and early death

were more frequent in the animals on elemental diets than in those on standard rations (24). The more completely hydrolyzed diets were correlated with lower albumin levels and increased frequency of positive blood cultures. Colon histology was abnormal in all. Bounous, et al (25) administered lethal doses of 5-FU (450 mg/kg and 50 mg/kg qd for 4 days) and found that rats acclimated to a variety of defined formula diets had a significantly shorter survival than rats maintained on normal rat chow.

Thus, although elemental diets may afford some protection against the gastrointestinal toxicity of clinical doses of 5-FU, the increased toxicity and mortality seen with higher doses is disturbing. The cause of death may be extraintestinal, as marked decreases in wbc count were noted in one study (25). The possibility of increased toxicity must be considered in any future trials using elemental diets in conjunction with chemotherapy.

Hematologic Toxicity

Rats fed an ad lib elemental diet have less wbc count depression after administration of a toxic dose of 5-FU than rats fed equicaloric amounts of standard rat chow (21). However, leukopenia wbc count $< 4000/mm^3$) developed in three of nine human cancer patients receiving standard doses of 5-FU (12.5 mg/kg iv qd for 6–9 days) with an elemental diet, but only two of 12 patients on a regular diet (22). Furthermore, rats given lethal doses of 5-FU exhibited significantly greater depression of leucocyte counts if maintained on defined formula diets rather than normal rat chow. This observation was made for several commercially available defined formula diets and was true whether the proteins were hydrolyzed or not (25). Again, these represent attempts to modify the composition of the diet rather than the quantity of nutrients ingested. Forced feeding with different diets might be more successful, but this certainly should be subjected to critical trials. It is possible that the increased granulocyte toxicity of lethal doses represents a greater kill of marrow cells, stimulated to proliferate by the elemental diet (16). Whether this ability of elemental diets to stimulate marrow activity could speed recovery from marrow insult is not known.

Response to Therapy

There are no published studies establishing an effect of enteral feedings on responsiveness to therapy. Such trials are presently being conducted at M.D. Anderson (Daly, J.M. personal communication).

CONCLUSIONS

Dietary manipulation is unlikely to be successful as primary therapy for most patients with the cancer cachexia syndrome. Its role in support of other therapies has been incompletely evaluated, but there are studies that suggest that proper use of this modality might lessen the gastrointestinal and hematologic toxicity of chemotherapy and radiation therapy. Ultimately, what nutrients are delivered will be at least as important as the route by which they are delivered.

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Complications of Total Parenteral Nutrition in the Cancer Patient

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Total parenteral nutrition (TPN) or iv hyperalimentation has been in clinical use for a decade following a concerted multidisciplinary investigative and applied effort for over 30 years. Since the inception of TPN at the University of Pennsylvania its clinical implementation has been rapid but without prior rigidly well-controlled clinical trials (1). This is understandable in light of its initial dramatic lifesaving successes in last-resort, critically ill patients. Following this initial clinical success, TPN has spread both in breadth and depth with expanded clinical indications accompanying the growth of expertise, experience, training, and education and the technical advances of improved hardware, software, and defined solution formulations. The overall benefits, cost, complications, and logistics are now being evaluated in a most preliminary and pilot fashion. TPN is a complex therapeutic modality with multiple independent variables influencing clinical outcome, complications, and costs. The clearest area in these muddy waters is the complications of TPN, particularly in the cancer patient. With respect to TPN complications, the evolutionary process included the initial period of enthusiasm, overextension, and application before the development of adequate experience, expertise, training, and education. The resultant complications generated an inappropriate retrogression to where nutritional support was being withheld from needy patients because of inordinate fears of its complications. With increasing education, training, skills, and expertise it is once again an expanding therapeutic modality with greatly decreased complication occurrences. About 150,000–200,000 patients/year in the United States receive TPN with approximately one-third being cancer patients (50,000–70,000 patients/year). This tremendous health care cost has been recently and more widely questioned on a superficial level.

The clinical dilemmas facing the oncologist and the clinical nutritionist are overwhelming. Numerous prospective studies (2–4) under varying conditions have documented that 50% of hospitalized patients are nutritionally depleted, some being at the preclinical level. A certain percentage of these patients undergo further iatrogenic depletion while under hospital care. In addition, some patients admitted to the hospital in a normal nutritional state undergo depletion during hospitalization. Often the clinical focus is inappropriately limited to the primary disease process, such as cancer, while the secondary manifestations are often ignored with deleterious aftereffects.

The Nutrition Support Service of the Hospital of the University of Pennsylvania with its team of 15 multidisciplinary individuals, nutritionally assesses 1400 new patients/year and 600–700 of these eventually receive TPN; 30%–50% are cancer patients at any one time. From this clinical perspective, we estimate that 10%–20% of the hospitalized patient population requires forced feeding to restore their nutritional status without any consideration of the suggestive or proven ancillary benefits of nutritional support. An obviously perplexing problem with the cancer patient is the question of whether his nutritional depletion is purely a manifestation of the primary disease, which will spontaneously resolve after successful antineoplastic therapy, or whether nutritional intervention will impact treatment success and therapy-related complications (5).

In a recent review of the reported complications of TPN over the past decade (6), several important concepts are apparent. The frequency, severity, and ease of diagnosis and treatment of TPN complications cannot objectively be assessed in an abstract fashion. Due consideration must be given to the multiple TPN-related benefits accrued by nutritional support as well as the multiple variables influencing the type, frequency, and severity of the TPN-related complications, and also to the economic cost of both the benefits and complications. Almost every possible complication of TPN has occurred and has been reported. The health care literature is disproportionately overpopulated with complication reports that most often reflect the quality of nutritional support rather than an inherent defect in the technique itself. The withholding of clinically indicated nutritional support in the depleted hospitalized cancer patient has detrimental effects on patient and is not justifiable on the basis of fear of its complications. Most TPN-related complications are iatrogenic, avoidable, and, in reality, an indictment of the quality of care rather than the technique itself. TPN has few inherent

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unavoidable risks. Basically, it is fluid and electrolyte therapy with additional nutrient substances, vitamins, and trace elements. It obviously requires a significant yet not overwhelming understanding of hormonal-metabolic events and the ability to manipulate these events in a beneficial fashion.

The risks and also their characteristics (frequency, severity, outcome) are dependent on multiple variables: (*a*) Patient population under consideration. Not only is the nutritional status of the given patient population an important determinant, but also the histologic type, stage of disease, and rate of progression, as well as the particular primary antineoplastic therapy being employed. (*b*) Competence of the nutrition support team delivering the care, including physicians, nurses, pharmacists, dietitians, and social workers. This pertains to both their individual and functional unit (education, training, expertise, and experience). (*c*) Often-overlooked competence of the institutional core staff, including the nursing, pharmacy, and dietetic services, as well as the physician house staff. This is often the prime determinant since nutritional care passes through this final common pathway. (*d*) Rapidity and degree with which newly developed techniques and clinical advances such as software, hardware, and clinical tricks are implemented. Rapid and knowledgeable implementation is particularly difficult with the recent rapid explosion of knowledge and the well-known defects in communicating and introducing new advances into clinical practice. (*e*) The organizational management system of the Nutrition Support Service as well as its overall goals, objectives, and major philosophies (table 1).

The multiple benefits of TPN are also very dependent on many variables beyond the delivery of all nutrients in adequate amounts, proportions, and rates. The patient population has considerable influence, as outlined above, as well as the management system and competence of both the core and Nutrition Support Service staff.

Many benefits of TPN have been espoused based on varying degrees of documentation and suggestive

TABLE 1.—Constituents of an ideal nutrition support service

1. Strong multidisciplinary expertise, interaction, and active participation at both the core staff and the nutrition support service level.
2. Intensive continuing educational efforts at both the core staff level and the nutrition support service staff level as well as their trainees.
3. Well designed multiple cross checks and retrospective audits in a system of quality control monitoring.
4. A career oriented commitment of a nutrition support service staff to the field of nutrition and active participation in research and education efforts at the local, regional, and national level.
5. Individual accountability for specific complications.
6. Specific responsible areas for the various disciplines participating in the nutrition support service activities.
7. A strong commitment to indepth effective interaction and communication departments involved in this multidepartmental, multidisciplinary activity.
8. A nutrition support service personnel should always remain members of their parent department; the resultant increased liaison and communication substantially enhances morale of the core institutional staff.
9. A commitment to providing a full time service, 7 days a week, on a 24-hour-a-day basis.
10. A recognition and implementation of the concept that an objective nutritional assessment is the first step in any rational nutritional support program.
11. Nutrition support service staff members should be 100% committed to nutrition support activities.
12. The core staff and the Nutrition Support Service staff must effectively interact with each other at considerable depth and maintain effective communication and educational exchanges.
13. The development of formal protocols and rigid adherence to same.
14. An awareness and recognition of the complexities of total parenteral nutrition both in the simple and complicated case and also in the critically ill at the other end of the spectrum.
15. A recognition of the labor and intensive quality of the nutrition support activities.
16. Continued constant high-level effort.
17. Continued vigilance and endurance.
18. Rapid and quality implementation of documented improvements in the field.
19. A system of restrictions and certifications of individuals on the core institutional staff who are participating in the nutritional TPN care of the patient.

evidence. Often overlooked is the axiom that nutritional support will not cure cancer and can only function as an adjuvant supportive therapy to successful antineoplastic therapy. Its potential benefits, which have been documented to varying degrees, include increased response rates to the antineoplastic therapy, decreased neoplastic therapy morbidity, improved quality of life, and obviously a restored or maintained normal nutritional status. Subjective impressions of the efficacy of nutritional support, real but undocumented, often exceed the documented efficacies obtained by rigidly controlled studies. In a particular subset, nutritional support is the only viable alternative and can be truly lifesaving. In addition to the vagueness of the benefits to the cancer patient, clinical applications of this modality in oncology have often preceded the obtaining of adequate education, training, experience, and expertise of the oncologist with resultant unnecessary iatrogenic complications.

The complications of TPN cannot be viewed adequately unless one considers the cost-benefit implications. TPN is expensive, mostly because of its labor-intensive quality at both the support service staff and core staff level, its increased duration of hospitalization, its requirement of increased level of care, as well as the more obvious costs for the necessary hardware and expendables. The increased demand on ancillary support hospital services, such as the laboratory and the radiology service, if often overlooked. In addition to nutritional therapy expenses, TPN complications are also expensive. Fortunately, they are usually easy to avoid and diagnose and rather simple to treat. On the other side, if certain cancer therapy-related complications with a nutritional component can be prevented by nutritional repletion and/or maintenance, the occurrence of these complications in the unsupported patient must also be considered, as these are expensive. Similarly, avoidable nutritionally-based, cancer therapy-related deaths also have a cost. Decreased response rates to cancer therapy, if they can be avoided by appropriate maintenance of nutritional status, are also expensive. Almost no reputable cost-benefit data exists, yet far-reaching decisions are often made based on subjective impressions.

The types of complications of TPN are multitudinous (tables 2–4). Fortunately, most are avoidable by an appropriately high level quality care in an organized management system. Few, if any, are particularly confined to the cancer patient population and a literature review finds little investigative work confined to the cancer patient population. Based on experience and available data, certain complications have a small semi-definable, inherently unavoidable risk potential in both the cancer and noncancer patient receiving TPN (table 5).

It is not the purpose of this paper to present an exhaustive review of all TPN complications, outlining their etiology, prevention, signs, symptoms, and metabolic and physiologic basis. Such detailed information is readily available.

TABLE 2.—Mechanical complications.

	Subclavian artery injury > ± hemothorax, hemomediastinum
	Subclavian vein injury
*	Pneumothorax
	Hydrothorax and hydromediastinum
	Brachial plexus injury
	Air embolism
	Thoracic duct injury ± chylothorax
*	Catheter intravascular malposition
	Catheter embolism
*	Subclavian/great vein thrombosis ± pulmonary embolism
	Great vein/cardiac perforation
	Catheter occlusion
	Arteriovenous fistula

TABLE 3.—Infectious complications

Fever
Catheter-related fever
Catheter tip infection
Catheter tip infection with bacteremia/septicemia
Catheter exit site infection
Non-catheter infection
Catheter tip infection (secondarily seeded)

TABLE 4.—Metabolic complications

Hyponatremia, hypernatremia
Hypoalkemia, hyperalkemia
Hypoglycemia, hyperglycemia
Hyperosmolar non-ketotic coma
Hyperchloremic metabolic acidosis
Azotemia
Hyperammonemia
Hypophosphatemia, hyperphosphatemia
Hypocalcemia, hypercalcemia
Hepatic dysfunction
Hypomagnesemia, hypermagnesemia
Essential fatty acid deficiency
Hypertriglyceridemia
Anemia
Hypoprothrombinemia
Plasma amino acid imbalances
Fluid overload
Zinc deficiency
Copper deficiency
Chromium deficiency
Folate deficiency
Vitamin B_{12} deficiency
Hypervitaminosis A
Hypervitaminosis D

TABLE 5.—Unavoidable complications

Type	Frequency range (%)
Mechanical	
Pneumothorax	1-2
Catheter intravascular malposition	2-5
Subclavian thrombosis	2-4*
Infectious	
Catheter-related fever	5-10
Catheter-tip infection	2-3
Catheter-tip infection + septicemia	1-2*
Catheter exit site infections	1-2
Metabolic	
Anemia	10

*Clinically significant.

Complications of TPN in the cancer patient must be viewed in several ways:

1. In the cancer patient, TPN versus non-TPN.
2. In the TPN patient, cancer versus noncancer.
3. In the noncancer patient, TPN versus non-TPN.

In the cancer patient, the only large-scale comparative study between TPN and non-TPN has recently been completed by the multi-institutional Adult TPN Study Group funded by the Diet, Nutrition, and Cancer Program of the National Cancer Institute (7). This study encompasses 341 cancer patients divided into protocol segments, according to tumor type, treatment regimen, and institution. Table 6 outlines the total number of patients studied as well as the numbers in subgroups randomized to TPN, randomized to control, and nonrandomized. As one can see from the table, 160 patients received TPN (125 randomized) compared with 126 randomized through the control arm. Of note are 10 patients in the randomized control group who crossed over to the TPN group for clinical indications such as nutritional deterioration.

Table 7 compares the frequency of complications between randomized groups. The data suggest several conclusions: TPN is a safe therapeutic modality in this patient mix undergoing aggressive antineoplastic therapy and can be accomplished on a multi-institutional basis under differing team formats and varying levels of expertise, education, experience, and training. A previously unappreciated high level of morbidity occurs in this cancer patient population-randomized control group. The institution of TPN adds little serious morbidity and no mortality in this heterogenous population and this small increment must be weighed against possible benefits of nutritional repletion and/or maintenance.

Several individual complications in the TPN group deserve further discussion and analysis. Although the patient study is completed, only tentative comments are appropriate since data analysis and interpretation are currently in progress.

Subclavian or great vein thrombosis is a recognized complication of TPN. It occurs in 4% of cancer patients receiving TPN (table 7). Contributing factors are the catheter composition with Silastic having decided advantages over the conventional polyethylene catheter. An additional risk factor is the occurrence of multiple catherizations of the subclavian veins. More questionable, with only little documentation, are the proposed etiologies of hypovolemia, intimal damage due to the hyperosmolar solution, duration of catherization, and lack of an antithrombotic agent in the TPN regimen. This complication is potentially serious, with the possibility of superior vena cava secondary thrombosis as well as pulmonary embolization. The treatment required involves anticoagulation, removal of the catheter with an appropriate culture, and the use of indicated antibiotics. The use of fibrinolysins and need for venography before reinsertion are still debated. A reasonable preventive approach includes the use of Silastic catheters for any patient receiving TPN > 3

TABLE 6.—Optimal nutritional support as an adjunct to cancer therapy in adults

Institution	Tumor Type	Therapy	Total patient entry	Randomized TPN	Randomized Control	Non-randomized
Pennsylvania	Ugi	Surgery	27	9	9	9
Roswell Park	Head & neck	Surgery	48	23	23	2
SUNY	Head & neck	Radiotherapy	35	15	14	6
New England Deaconess	Abdominal pelvic	Radiotherapy	27	8	6	13
MD Anderson	Non-oat cell lung	Chemotherapy	55	13	13	29
MD Anderson	Testicular	Chemotherapy	44	18	18	8
Boston University	Abdominal & pelvic	Radiotherapy	7	1	1	5
Emory University	Colon	Chemotherapy	50	21	25	4
MD Anderson	Ugi & non-oat cell lung	Chemotherapy	48	17	17	14
Totals			341	125	126	90

TABLE 7.—Adult TPN study

Complication	Randomized TPN	Randomized control	P<
Fever	61/100 (61%)	40/102 (39%)	0.003
Non-catheter infections	26/103 (25%)	26/106 (25%)	NS*
Catheter related fever	? /100 (?)	? /102 (?)	—
Catheter exit site infection	4/101 (4%)	1/10 (10%)	—
Catheter tip infection	6/97 (6%)	1/9 (11%)	—
Catheter tip infection + sepsis	6/100 (6%)	0/10 (0%)	—
Unexplained fever	? (?)	? (?)	—
Pneumothorax	0/100 (0%)	0/10 (0%)	—
Hemothorax	0/100 (0%)	0/10 (0%)	—
Subclavian vein thrombosis	5/125 (4%)	0/10 (0%)	—
Other catheter complications	6/96 (6%)	0/6 (0%)	—
Hyperalkemia	4/104 (4%)	1/107 (1%)	NS
Hypoalkemia	5/104 (5%)	2/107 (2%)	NS
Hypophosphatemia	2/104 (2%)	3/106 (3%)	NS
Hyperosmolar coma	0/104 (0%)	0/107 (0%)	NS
Acidosis	2/104 (2%)	1/107 (1%)	NS
Anemia	29/100 (29%)	18/102 (18%)	0.09
Hepatic dysfunction	4/100 (4%)	1/101 (1%)	NS
Congestive failure	6/103 (6%)	2/108 (2%)	NS
Pulmonary dysfunction	31/100 (31%)	21/102 (21%)	0.13
Death within 30 days	7/100 (7%)	5/102 (5%)	NS

*NS=Not significant

weeks and perhaps, in the future, the use of Silastic catheters for all patients when the hardware technologic advances are achieved for percutaneous introduction. Obviously important are strict aseptic catheter care and radiographic confirmation of the catheter tip position after insertion. The use of heparin in a TPN regimen has been much debated with conflicting results.

The second set of possible complications for the TPN cancer patient includes infections. The major one is catheter tip infection and secondary bacteremia with occasional clinical septicemia. Obviously the control non-TPN cancer patient does not have this potential risk. The incidence of documented positive catheter tip infection in this study was 6% of the randomized TPN group and of all TPN patients (table 8). In addition (and sometimes associated) were localized infections at the catheter exit site (4%). In this complex investigative area, one must discern the subtle differences between a positive catheter tip culture, catheter tip infection with bacteremia, clinical septicemia, catheter exit-site infection, catheter-related fever, and unexplained fever. Complicating the situation are the often present infections (25%) with bacteremias and clinical septicemia from other sources which may secondarily seed the indwelling catheter.

Six percent of the TPN cancer patients had other catheter complications. On detailed analysis they were often simple mechanical problems easily corrected with no clinical sequelae (three catheter occlusions, one catheter intravascular malposition, one administration set leakage, one catheter extracted by patient); 50% of these problems occurred in one protocol segment which had 10% of the randomized TPN patients.

The mortality rates during the active TPN treatment period and equivalent period in the control patient were essentially no different: five of 102 (5%) versus seven of 100 (7%).

TABLE 8.—TPN complications in cancer patients: fever and infection

Complication	Rand-cont cross over	Rand TPN	Mal TPN
Fever	42/108 (39%)	64/102 (62%)	14/18 (78%)
Non-catheter infections	26/106 (25%)	26/103 (25%)	9/18 (50%)
Catheter-related fever	? /10 (?)	? /103 (?)	? /19 (?)
Catheter exit site infection	1/10 (10%)	4/101 (4%)	0/19 (0%)
Catheter tip infection	1/9 (11%)	6/97 (6%)	0/16 (0%)
Catheter tip infection — bacteremia	0/10 (0%)	6/100 (6%)	0/19 (0%)
Unexplained fever	? (?)	? (?)	? (?)

The increased frequency of clinically significant anemia in the randomized TPN cancer group is noteworthy and merits attention and discussion. Its causes are often multiple but primarily include losses through increased phlebotomies, unrecognized nutrient deficiences (folic acid, vitamin B_{12}, iron, copper), and a dilutional effect secondary to expansion of plasma volume associated with TPN. Further data analysis and interpretation are necessary to better define this problem, including a confirmation of this clinical impression by an evaluation of hemoglobin and hematocrit levels.

The increased incidence of fever in the TPN cancer group also deserved special consideration and analysis. As noted previously, 25% of both the randomized control group and the TPN group had documented infections at distant sites which leaves 11% of the fevers in the control group unexplained. In the TPN group, 61% of patients experienced a fever during their TPN course, which can partially be explained by the 25% of patients who had infections at a distant site, the 6% of patients who had catheter infections, and the 4% of patients who had infections at the catheter exit site. This still leaves 30% of the patients with fever with an unexplained etiology. Fischer and his group (8) at the Massachusetts General Hospital have analyzed this problem in a mixed patient population including some cancer patients, and have pointedly observed a similar phenomena in this mixed TPN patient population. In their series of 150 patients, about 50% of the patients had an episode of fever during their TPN. Thirty-five percent had a fever originating from a well-documented infection at a distant site. In addition, 4% had a well-documented catheter infection by positive blood cultures, positive catheter tip cultures, and the disappearance of fever after catheter removal. In addition, another 9% of patients had a noninfected catheter-related fever that resolved after catheter removal, without any microbiologic contamination or infection. In this series, 20% of all TPN patients had a fever that was unexplainable . The removal of a TPN catheter because of a fever is often unnecessary and certainly exposes the patient to the additional risks of another percutaneous subclavian catherization, unless the catheter is changed over a wire. A similar series has been documented by Copeland et al at the University of Texas at Houston and the MD Anderson Cancer Institute (9). In this study of 40 catheters in 35 patients, 4 were suspected and were removed with a prompt decline of the fever without any evidence of microbiologic contamination or infection (10% catheter-related fever). In addition, three patients (7.5%) had culture-positive catheters without any clinical sequelae such as bacteremia or septicemia.

With a multifactoral intensive effort to maintain catheter asepsis, we have recently documented its success in a severely compromised host, the adult leukemia patient undergoing induction chemotherapy with its associated granulocytopenia and thrombocytopenia (10). The catheters remained in place for an average of 4 weeks and all patients were granulocytopenic with wbc counts $< 500/mm^3$ for a mean of 4 weeks during which the catheters were in place. Fifteen of the 25 patients (60%) were infected with bacteremia from a distant source, but in only one instance (3.1%) was the catheter itself infected secondarily. None of the catheters was infected primarily. Fifteen percent of the patients died with the catheter in place and in 9 an autopsy was available to confirm the subclavian catheter being free of infection and thrombosis.

Although not statistically significant, the incidence of cardiopulmonary dysfunction in the TPN cancer patient may be increased over the non-TPN cancer patient. Fluid overload and increased O_2 consumption and CO_2 production may be mostly responsible.

An alternative technique for providing adequate nutrients to the cancer patient is enteral forced-feeding or enteral alimentation. Its role is more limited since the required functional gastrointestinal tract may be impaired due to the malignancy or its various treatments (surgery, chemotherapy, radiotherapy, etc). TPN and enteral alimentation are complementary, not competitive techniques and are occasionally employed in a combined nutrition support program. The prime clinical objective is to provide adequate nutrients to the cancer patient and the delivery route is of secondary importance. Enteral alimentation avoids the catheter-related mechanical and infectious complications of TPN, but it has its own complications and difficulties with clinical efficacy. If *adequate* nutrient intake can be *safely achieved* via the gastrointestinal tract, this delivery technique is the procedure of choice.

CONCLUSION

TPN is as safe in the cancer patient as in the non-cancer patient. TPN adds minimal increased risks to the cancer patient, mainly in the form of catheter sepsis and great vein thrombosis and possibly a requirement for increased attention to anemia and cardiorespiratory care. The previously unappreciated metabolic and clinical complications in the non-TPN cancer patient are substantial. The costs and risks of the complications of TPN plus the cost of uncomplicated TPN must be balanced against the benefits and costs of nutritional support for repletion or maintenance in the cancer patient.

This area requires considerably more well-controlled, well-focused, and well-designed studies to examine the complex multivariant nature of the problem. Clinical experience and documented studies justify the above conclusion, which may help eliminate the withholding of adequate nutritional support to the cancer patient

because of an inordinate fear of its complications. This does not justify the use of TPN in the cancer patient; however, it should not be used to withhold such potentially beneficial therapy.

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Nutritional Support and the Immune System in Cancer Management. A Critical Review.[1]

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SUMMARY

The nutritional state of the cancer patient is still a poorly defined parameter that most probably presents specific differences when compared with other states of denutrition. By definition, the immune response is altered in the denutritive condition. Factors such as amino acids, lipids, insulin, vitamin A, vitamin C and, zinc should be studied in more depth since existing studies have already shown that changes in plasma levels of these factors can modulate the immune response. Present information on hypernutrition is clearly inadequate and often difficult to evaluate, since it is based on nonrandomized trials in cancer patients, and for whom the relationship between nutritional state and the associated immune response was not clearly established. In addition, the effects on lymphocyte subpopulation functions within this context have not been adequately studied. These and other factors lead us to believe that nonspecific global parenteral hyperalimentation, as presently employed, is of limited interest and also expensive. We propose a more specific approach to nutritional therapy that would lead to a more specific modulation of the overall immune response.

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The role of the immune system in the development and control of cancer is widely documented. Nevertheless, this role remains poorly defined due, in large part, to the number of different cell types that come into play in the immunological defense mechanism and the interactions of these different cellular participants. Despite recent progress in the study of different human lymphocyte subpopulations (1,2), the precise function of these cells and their integral roles remain obscure. In addition, when one considers additional cellular parameters such as monocytes, macrophages and polymorphonuclear cells, the anticancer defense mechanism as a whole becomes a complex investigation.

At least during certain stages of development, cancer is associated with denutrition that is more or less pronounced, depending on the type of cancer and its localization (3,4). Obviously, this nutritional state will deteriorate faster for cancers affecting the alimentary canal. Some cancers, such as those of the lung, are routinely associated with marked and rapidly evolving denutrition. Although numerous studies have been conducted on these denutritional states, the neoplastic denutritional condition has not been well characterized. It now appears that, little by little, the denutritional condition of the cancer patient is becoming, at least quantitatively, more precisely defined.

Several authors have already shown that the nutritional state can alter the immune response (5-9). Moreover, nutrients such as amino acids (10), lipids (11-14), and hormones such as insulin (4,15) can alter this response in a positive or negative manner. Given that the cancer patient presents a denutrition, this will most likely result in a decreased immunological defense potential concomitant with an already tumor-induced demand on the patient's immunological capabilities, all of which involve an interplay and probable synergy of poorly understood mechanisms.

Although there are numerous reports on immunological modifications as a function of the nutritional state, few studies have been made on the tumor-bearing patient. Furthermore, there is no report on the relationship between recently defined lymphocyte subpopulations and the denutritional state in this type of patient. Most investigations have concerned them-

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selves with the correlation between cancer and the immunological status of the patient, without establishing any intimate relationship between the denutritional and immunological states of the same tumor-bearing patient. It is precisely this relationship that is explored in this brief review of present investigative efforts.

NUTRITIONAL STATUS OF THE CANCER PATIENT

Despite numerous studies on the denutritional state, the nutritional status of the cancer patient has received relatively little attention until recently. Even so, there has been no study of this perspective within the context of cancer as a disease process per se. Although denutrition can occur as a result of the cancer itself, it can also arise as a consequence of therapy, whether surgical, radiotherapeutic, or medical.

The denutritional state can present as an anorexia accompanied by a loss of weight (indicative of cancer). For certain tumors, for example Hodgkin's and lung cancer, this weight loss is associated with a poor prognosis. Alternatively, this loss could be linked to a tumor somewhere in the alimentary canal. It should be kept in mind that hypermetabolism can occur during tumor growth and/or infection.

Some recent studies on cachexia in the cancer patient have shown that there is loss of insulin sensitivity. Other studies show that insulin can stimulate appetite and may act as a tumor inhibitor (4,15). At present, these findings are the subject of wide-scale research efforts. Furthermore, some authors report significantly increased plasma free fatty acid concentrations during cachexia (3). Generally speaking, the cachexic state in the tumor-bearing patient is characterized by progressive lipolysis associated with increased gluconeogenesis, associated with an insulin-resistant condition (16–18). Other sugar and amino acid metabolic aberrations have also been suggested.

These problems as a whole attest to the fact that the consequences of denutrition in the cancer patient are far-reaching, complex, and therefore should be resolved, a priori, by employing presently available parenteral alimentation techniques. However, present nutritional protocols (19–22) contain an overall number of calories considered to be sufficient to re-establish normal weight values for the tumor-bearing patient, ignoring both the undesirable effects of such therapy and the precise metabolic requirements of the individual, as well as the tumor itself. Selective nutritional programs are becoming more and more indicated as precise information becomes available on the metabolism of such patients. It should also be kept in mind that as metabolism in the cancer patient is better understood, the better its immunological repercussions can be appreciated. For example, it has already been shown that lymphocytes carry surface receptors for insulin and are extremely sensitive to variations in the cholesterol/phospholipid ratio (11). This knowledge has led to the development of in vitro tests capable of better evaluating the result of modifications of these parameters and consequently evaluating subsequent effects on the immune system of the cancer patient.

Nutritional differences are usually anticipated during the course of most therapies for the cancer patient, for example, digestive tract resection followed by intestinal atonicity leading to significant nutritional change. This is particularly noted for large resections of the small intestine and pancreas. The same considerations can be applied following radiotherapy, especially when large abdominal irradiation is associated with chemotherapy. This frequently results in nausea, vomiting, mucosal ulcerations, secondary atrophy of the mucosa, or retarded intestinal transit. This can precipitate secondary ileus leading to a dehydration that is difficult to correct, if early diagnosis and treatment are not made. This condition is aggravated where preexisting denutrition exists.

CHOICE OF NUTRITION FOR THE CANCER PATIENT

Since a precise analysis of the nutritional state of the cancer patient is not possible, the problem will therefore be approached in general terms and from a simplistic point of view. A priori, the cancer patient presents as an individual who has already lost a more or less significant amount of weight and is undergoing aggressive therapy. Such patients will always exhibit weight loss. This condition in itself can give rise to certain complications, such as retarding or cessation of radio- or chemotherapy, rendering the patient a poor surgical risk due to his denutritive state. The rationale should therefore be the following: when faced with a potential or real denutrition, the physician should decrease surgical risk to the patient and/or augment the patient's tolerance for therapeutics such as radiotherapy (especially abdominal irradiation) and chemotherapy by iv administration of enough calories to avoid additional weight losses, or even place the patient into an anabolic situation to help him regain part or all of his weight deficit. This approach has led to parenteral nutrition by either superficial or deep-vein catheterization (19–22). This technique allows a relatively long-term parenteral nutrition infusion time without any major inconvenience to the patient other than protection of the injection site during and between infusions. Nevertheless, risk of infection is present where a sterile technique is not scrupulously followed. Properly used, this method can be used to administer 2000–4000 kcal/day, allowing the patient to reach his postoperative period without threat of denutrition and also rendering previously inoperable patients operable.

Despite the obvious advantages of this technique, a certain number of inconveniences or unknown factors should be considered. To begin with, this therapy is demanding on the patient and relatively expensive. In addition, at present there has been no randomized study to ascertain if normo- or hyperalimentation actually ameliorates the patient's situation, except for the surgical context mentioned above. Several works have been published showing that in nonrandomized groups, patients treated by parenteral nutrition better tolerate certain aggressive therapies, particularly chemotherapy (23–30). Furthermore, these patients maintained a better blood profile with a higher incidence of remission. These same conclusions were reported by Issell et al (31) following a randomized study of chemotherapy-resistant tumors. In contrast, highly chemosensitive tumors did not seem to respond in the same fashion (32). Results from patients receiving pre- or post operative parenteral nutrition over several weeks gave no clear indication whether the risk of loco-regional relapse or metastatic dissemination was higher than that found in control groups not receiving this therapy. In fact, some research has shown that parenteral nutrition may facilitate tumor growth by different mechanisms, possibly involving an increased number of cells drawn into the cell cycle at the tumor site or by direct action on the immune response per se (33).

Therefore, great care must be exercised when nutritional therapy is administered outside of a well-conceived randomized trial context, not only in an effort to control specific known effects that may come into play but to try to avoid any untoward consequences as a result of poorly understood mechanisms involving the immune system. It has already been shown that the immune response can be modulated by certain vitamins, such as A and C, some metals such as zinc (34,35), lipids (11–14), and probably by amino acids (10). It has further been reported that cytotoxicity strongly depends on the presence of both glucose and insulin (4,15).

EVALUATION OF THE EFFECTS OF NUTRITION ON THE IMMUNE RESPONSE

Alteration of the immune response has usually been studied in patients presenting malnutrition (5–7,9,37–41). The levels of properdin, complement, interferon, and transferrin were decreased in nutritional deficiency. Impaired phagocytosis has also been reported for some malnutritive states. We have already mentioned that deficiencies in vitamin A (36), vitamin C, and zinc (34,35) can alter immune response. More recently, decreased circulating thymic hormone levels (42) have been observed in malnutrition. This may be related to thymus dysfunction, as previously noted for kwashiorkor. Malnutrition can be characterized by significant thymic change, including a reduced organ weight, changes in cellularity, and modification of Hassall corpuscles. In addition, lymph nodes and spleen present depleted paracortical and periarteriolar zones as well as primary follicular areas and germinative centers. There is a decreased PHA response accompanied by a reduced response to certain antigens both in vivo and in vitro. The number of circulating B and T lymphocytes is usually normal or low. Total complement and its components (except for C4) are reduced.

It is often difficult to discern the respective roles played by the tumor versus denutrition when establishing the immune status of the cancer patient. However, recent findings reported by Gertner (7) demonstrate a positive correlation between the number of T rosettes and serum albumin levels in cancer patients, suggesting that immunological changes in these patients may be associated with the nutritional state. In another study Weeks and Ozelc (8) showed that animals suffering from denutrition show no immunological response to BCG extracts when compared to animals maintained on a normal diet. This again suggests that there is probably an intimate relationship between immune response and nutritional state.

Indirect evidence, from both animal and human studies has shown that hyperalimentation alone can ameliorate the immune status of the tumor-bearing host. Unfortunately, none of the above studies was performed as randomized trials with a untreated (no hyperalimentation) or placebo group included for comparative analysis. However, using iv hyperalimentation, Daly et al (43) were able to re-establish normal weight as well as ameliorate immunocompetency in tumor-bearing denutritive animals, without any apparent stimulation of tumor growth. Similarly, Copeland et al (38) have shown that iv hyperalimentation significantly improves the hypersensitivity response to different solid tumors treated by surgery, irradiation, or chemotherapy. They further report that their surgical patients demonstrating positive skin tests showed few complications during their postoperation period when compared to patients who continued to demonstrate negative skin tests. In their chemotherapy group, the same authors report that only those patients whose skin tests became positive during nutritional therapy responded to chemotherapy, thereby benefiting from an improved prognosis relative to those patients whose skin tests remained negative. Similar results were also noted by Dionigi et al (40) who showed that concentrations of serum immunoglobulins G and M as well as complement fraction C3 returned to normal along with an improved primary immune response to sheep red blood cells following hyperalimentation. The same authors noted restored phagocyte chemotactic re-

sponses although the PHA response remained unchanged. Their results therefore suggest that parenteral nutrition may be capable of re-establishing certain immune responses in animals suffering from malnutrition.

In our experience (28–30), different chemoresistant solid tumors (essentially epidermoid and glandular digestive tract tumors) showed significantly improved chemotherapeutic response and decreased toxicity for patients on nutritional therapy when compared to a matched tumor group not receiving this treatment. Our protocol consists of iv administration of 1550 kcal/day; each day the patient receives chemotherapy following this protocol. We also observed amelioration of certain immune responses, notably a significant increase of positive skin tests and increased levels of auto-rosette forming cells. In cases where skin tests became positive and auto-rosette forming cells increased above 15% level under hyperalimentation, the patient responded better to chemotherapy and had a better prognosis than patients whose skin tests remained negative and auto-rosette forming cells were less than 15% (table 1).

Certain points should be kept in mind. In our study we only evaluated the overall immune response during a given nutritional protocol whose sole intention was to augment patient weight. This therapy was nonoriented in the sense that it was not geared to real variations in metabolism of the cancer patient. Certain recent results, whose implications have yet to be entirely understood, should not be overlooked; namely, modifications that may arise in zinc, vitamin A, or vitamin C metabolism as well as in glucose and, in particular, insulin metabolism. In fact, it has been shown that vitamin A, vitamin C, and zinc play an important role in immune response modulation and that glucose may participate in certain types of T cell cytotoxicity. It should be recalled that lymphocytes bear receptors for hormones such as serum thymic factor (42) (which is reduced during denutrition), insulin, or other hormones whose role(s) during the denutritive state has yet to be clarified.

Lastly, the role of lipids in the immune response is related to membrane fluidity which in turn can effect membrane receptors for antigen. Alterations of this fluidity in response to the cholesterol/phospholipid ratio can therefore become an important factor. All these parameters will require a more in-depth analysis to resolve such questions as why amino acids are immunostimulatory for some investigators, immunodepressive for others, and for still others a source of retardation or stimulation of tumor growth. Thus, the problem is complex, since all of these circulating elements (lipids, sugars, amino acids, certain metals, vitamins) can be markedly changed during the course of denutrition, particularly in the case of cancer. At least in theory, all of these substances possess potential immune modulatory capabilities vis à vis the immune response. Consequently, re-establishment of the immune response could partially depend on the re-establishment of normal or subnormal metabolism.

CRITICISMS AND PERSPECTIVES

What has been established is that nutritional disturbances can be observed for disease, whether neoplastic

TABLE 1.—Effects of peripheral intravenous nutrition on immunological functions*

		PIVN group	Matched group	*P* value
Positive skin tests† (•)	No. of patients	81	79	
	Prestudy %	29	26	NS‡
	Pre 3rd course %	34	31	NS
	Pre 5th course %	45	28	< 0.05
Auto-rosette forming cells (< 15%)	No. of patients	31	27	
	Prestudy %	19	21	NS
	Pre 3rd course %	25	22	NS
	Pre 5th course %	29	17	NS

*In this table, we can observe a significant increase in the number of patients with positive skin tests and a percentage of auto-rosette forming cells superior to 15% increase in the PIVN group.

†Positive skin tests = induration reaction ≥ 2.5 cm (mean of length and width) noted for at least two skin tests (delayed hypersensitivity: Merieux system).

‡NS = not significant.

or not, and can give rise to significant alterations in the immune response, including both macrophage as well as B and T cell-related immune responses. In addition the thymus is often atrophied, giving rise to decreased circulating thymic factor. It is difficult to ascertain whether the non-neoplastic denutritive state can be completely superposed for cancer patients. If cancer patients can be shown to exhibit specific metabolic perturbations involving amino acids, lipids, sugars, or insulin, the individual role of each element in the immune response could be much more extensively investigated.

In a less obvious manner the role of zinc, vitamin A, or vitamin C will have to be better understood in order to appreciate their influence on the immune response.

In reviewing the literature for the last 5 years, one is struck by the absence of any well-designed, randomized study. In our mind, there is no peremptory evidence that hyperalimentation benefits the tumor-bearing patient. In fact, it is possible that, depending on whether a tumor is chemosensitive or not, nutritional therapy may or may not have a favorable effect. Although this later finding was based on randomized trials, it is still too early to draw definite conclusions. If hyperalimentation, by normalizing certain metabolic parameters and re-establishing patients' weight, can improve certain immune responses, it is still not possible to say if this would include an amelioration of favorable immune responses in the tumor patient. Certain unpublished clinical and animal results lead us to believe that facilitation of tumor growth instead of improved patient health may be related to the schedule of parenteral hyperalimentation and the precise point where therapeutic intervention occurs. This should evoke careful interpretation of results presently available with the decision to retain hyperalimentation based on the following questions:

1) Does hyperalimentation present a risk for the tumor patient? Under certain conditions does it accelerate or facilitate tumor growth by whatever mechanism, whether directly at the level of the tumor itself by bringing more cells into the cell cycle or by indirect action involving the immune system?

2) If hypernutrition is found to facilitate tumor growth, is there a period during patient treatment when this action does not exist, where therapeutic efficacy can be enhanced either by manipulating the tumor cycle and/or the immune response? For example, we already know that chemotherapy is more efficacious when more tumor cells are drawn into the cell cycle; or, the enhanced response to chemotherapy when the patient presents a satisfactory response to skin tests.

3) What are the precise characteristics of denutrition in the cancer patient?

4) What role is played by amino acids, sugars, insulin, and lipids in the modulation of the immune response?

5) Can certain metals such as zinc, or vitamins such as A and C alter immune response?

These questions, seemingly obvious, are seldom handled directly in the literature even though their resolution would promote a deeper understanding of the relationships existing between nutritional changes and the immune response, leading to manipulation of this same response in an effort to control tumor evolution. Toward this goal, in vitro tests should be developed to help evaluate the in situ as well as the overall immune response. Although this second concept appears obvious, the first consideration will necessitate the development of tumor clone techniques (44).

Whatever the different factors involved, the situation requires immediate action since parenteral hyperalimentation in its present form appears to exhibit a relatively limited usefulness for the cancer patient and will probably find restricted application in the future due to the cost involved.

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Total Parenteral Nutrition as an Adjunct to Chemotherapy of Metastatic Colorectal Cancer[1]

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SUMMARY

A randomized study was performed in advanced colon cancer to test the effectiveness of total parenteral nutrition (TPN) in maintaining and improving nutrition, to examine the effects of TPN on tumor growth, and to determine if TPN altered chemotherapy response rates, treatment tolerance, and survival. Forty-five patients on identical chemotherapy were randomized to TPN versus ad libitum feeding.

TPN was well tolerated. No clinical or tumor marker evidence suggesting neoplastic growth stimulation was obtained. Chemotherapy-related complications and chemotherapy responses did not differ between the two groups. TPN had little effect on performance status. TPN patients gained an average of 2.9 kg before chemotherapy, but triceps skinfold and mid-arm muscle area did not change significantly during TPN. Survival did not improve with TPN. We conclude that current techniques of TPN are of limited benefit in advanced colon cancer. A small subset of patients with short-gut malabsorption may be helped. Further study is needed to determine the mechanisms of cancer undernutrition and to refine nutritional supplementation techniques on the basis of these mechanisms.

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Our group recently described progressive depletion of adipose tissue, skeletal muscle, and visceral protein [protein calorie undernutrition (PCU)] in advanced cancer patients (1). There was a significant correlation between the degree of PCU and survival: the more severe the PCU, the shorter the survival.

Since hyperalimentation has been successful in noncancer cachexia (2–4), it is possible that such techniques might benefit the undernourished cancer patient. This extrapolation rests on two important assumptions: (*a*) that nutritional support will correct the cachexia of cancer as effectively as that of noncancer; and (*b*) that nutritional support will not accelerate tumor growth.

We have, as part of a multi-institutional study (NIH contract NO1-CP-65802, Segment 8, Adenocarcinoma of the Colon) compared TPN versus ad libitum feeding in advanced colon cancer patients on chemotherapy. Our aim was to investigate the effectiveness of TPN in maintaining and improving nutrition in colon cancer, to examine the effects of TPN on tumor growth, and to determine if TPN altered response to chemotherapy, treatment tolerance, or survival.

PATIENTS AND METHODS

Patients

From February 1977 to June 1978, 50 patients with metastatic colon carcinoma were entered into the study; all were accrued from Emory University Hospital or from the Winship Clinic for Neoplastic Disease of Emory University. Entry criteria are listed in table 1.

All patients had a metastatic workup which included complete history and physical examination, chest x-ray, hematology profile and SMA-12, radioisotope liver and bone scan, and tumor marker assay (CEA) (5,6); abdominal CT scans were performed when appropriate. Locations of existing lesions were recorded

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TABLE 1.—Criteria for study entry

1. Histologically verified colon cancer.
2. Age greater than 15 years.
3. Life expectancy of at least 4 weeks.
4. No contraindications to TPN; severe heart or renal disease, fistulae, uncontrolled diarrhea or vomiting, psychological instability, resistant infections.
5. Measurable lesion(s) present or elevation of tumor markers.
6. No surgery, radiation or chemotherapy for 2 weeks prior to study entry.
7. Recovery of peripheral blood counts from previous therapy.
8. Surgery or radiation would not give significant palliation.
9. Less than 24% weight loss from premorbid level.

as (*a*) primary tumor (*b*) recurrent tumor (*c*) local extension (*d*) regional lymph node involvement or (*e*) specific metastatic site. Accessible lesions were measured (length x width in cm). Zubrod performance status was determined (table 2), and profile of mood states (POMS) obtained (7,8).

Baseline nutritional parameters were measured, including weight (kg), height (cm), triceps skinfold (TSF) (mm), mid-upper arm circumference (MAC) (cm) and 24 hour urine creatinine to height (cr/ht) (mg/cm). MAC and TSF were converted to mid-arm muscle area (MAMA) (cm^2) according to the equations of Jellife et al (9).

Experimental Design

Patients were placed in three weight-loss strata: (*a*) 0%–6%; (*b*) > 6%–12%;(*c*) > 12%–24% (based on premorbid and on study weights). Randomization was performed within each weight loss stratum to TPN or ad libitum feeding (control) via sealed envelopes provided by the support contractor. Patients were not stratified on the basis of sites of metastases.

TPN patients were to receive a minimum of 14 days of central hyperalimentation followed by a 5-day course of chemotherapy; TPN was continued during chemotherapy. Control in-patients were offered regular hospital diets and ate their usual diets at home. Chemotherapy began immediately following randomization in the control group.

TABLE 2.—Zubrod Performance Scale

0 = No symptoms
1 = Symptoms but fully ambulatory
2 = Requires nursing assistance; in bed ≤ 50% of normal day
3 = Bedridden > 50% of normal day
4 = Bedfast

All patients received 5-FU, 20 mg/kg/day (lean body weight), by constant 5-day infusion every 4 weeks. Methyl-CCNU, 75 mg/m^2 was given every course. Doses were decreased as necessary for blood count suppression, nausea, vomiting, and/or stomatitis.

Central subclavian hyperalimentation was delivered by infusion pump to supply at least 35 kcal/kg/day and 0.2-0.3 gm nitrogen/kg/24 hr. Trace minerals (as Zn, Cl_2, $CuCl_2$, $MnCl_2$, $CrCl_3$, NaI) and multivitamins were added to the TPN amino acid and glucose solution in amounts specified by standard protocol (10). Patients also received parenteral multivitamins (one 5-ml ampule MVI concentrate daily), vitamin E (10 mg/week im), folic acid (10 mg/week im) and vitamin B12 (1 mg/month im). Major minerals and electrolytes (Na, K, Cl, Ca, P, Mg) were given as necessary to maintain normal serum levels. Lipids were not routinely given by mouth or parenterally. Oral intake was permitted as desired and recorded.

Catheters were placed by a vascular surgeon using standard antiseptic techniques. Dressings were changed at least every other day by nurses experienced in TPN. One liter of TPN solution was given during the first 24 hours then increased to desired levels over the next 2–3 days; at the end of TPN, the flow was dedreased over 2 days to assist the transition back to oral feedings.

During TPN, patients were monitored daily for glycosuria, and three times weekly for hyperglycemia, hyperosmolarity, and electrolyte imbalance. Appropriate medical management was instituted for any abnormalities. If catheter-related sepsis was suspected the central line was pulled and its tip cultured. TPN was performed only once unless the patient lost weight to his pre-TPN level and in the judgment of the investigators was still a candidate for TPN.

Control patients' intake was measured by project dieticians while in the hospital; 3-day diet diaries were completed by TPN and control patients monthly as outpatients. Clinical, nutritional, and biochemical studies were repeated at 4-week intervals in all patients (at the time of rehospitalization for monthly chemotherapy). Survival was calculated from date on study.

Statistical methods

The x^2 test for differences in proportions or Fisher's exact test was used to compare proportions between the TPN and control groups. The paired t-test was used to compare pre/post mean levels, eg, baseline wbc count versus pre-chemotherapy wbc count in the TPN group. Mean levels of separate groups, eg, baseline wbc count for TPN versus baseline wbc count for controls, were compared using t-tests or the two sample Wilcoxon rank sum test (11).

Comparisons of two survival curves were done using Gehan's generalized Wilcoxon test (12). All *P*-values reported using the generalized Wilcoxon test are one-sided. Poststratification comparisons of survival curves utilized the logrank test (13). A *P* value of 0.5 or less was considered significant.

The experimental design is summarized in figure 1.

RESULTS

Of the 50 patients accrued, one refused to continue TPN after 1 week, surgeons were unable to place the subclavian line in another, a third died before TPN was begun, and two had lost more than 24% of their premorbid weight, leaving 45 evaluable randomized cases. Clinical data of this patient population are given in table 3. The two patients with more than 24% weight loss received TPN but are not included in this statistical analysis.

1. *Baseline comparisons.*—Of the variables in Table 3, all taken at baseline, none was significantly different between the TPN and control groups. Other variables were also not significantly different: hematocrit, platelets, circulating wbcs, polys, lymphocytes, weight, TSF, MAMA, and albumin.

2. *Complications during TPN.*—TPN lasted an average of 3½ weeks (range 8–36 days) and was generally well tolerated. One patient developed septicemia (staphylococcal) after 16 days of TPN but responded promptly to antibiotics; this patient was suspected of manipulating the catheter and dressings; TPN was discontinued. Three patients experienced fluid overload but only one had to stop TPN (after 8 days). The other two responded to decreased NaCl delivery and diuretics. Two other required insulin for asymptomatic hyperglycemia and another, an elderly man, had a stroke of uncertain etiology during TPN and TPN was stopped. No patient had pneumothorax or clinically apparent pulmonary embolus. The three patients in whom TPN was stopped because of complications are included in the analysis; none of these died as a direct result of TPN.

3. *Clinical complications during the first chemotherapy period, TPN and control patients.*—Dysphagia and oral ulcerations (mucositis) occurred in only one or two patients in each group with the first chemotherapy dose (prechemotherapy 1 to prechemotherapy 2 (fig 1)). One control patient became septic. There were no statistically significant differences in severity of nausea and vomiting or pain. Hepatic complications (precoma and coma) occurred in three TPN patients and in no control patients. Constipation was significantly more frequent in TPN patients ($P = 0.0001$) but was mild.

4. *Response to chemotherapy.*—Three of the 20 TPN patients and three of the 25 control patients had greater than 25% shrinkage in the products of perpendicular diameters of measurable lesions. Duration of

TABLE 3.—Baseline comparison of TPN and control groups

	TPN (20)	Control (25)
Mean age	55	61
Male	11	8
Female	9	17
Weight loss strata (%)		
0–6	40	40
6–12	25	28
12–24	35	32
Metastatic sites (%)		
Liver	85*	68*
Abdomen not liver	5	24
Bone	35	12
Brain	5	0
Lung	65	40
Lymphatic	60	60
Liver chemistries (% abnormal)		
Alkaline phosphatase	75 (mean = 259)†	72 (mean = 224)
SGOT	35 (mean = 39) ‡	28 (mean = 50)

*By radioisotope scan.
†Normal up to 100 mu/ml.
‡Normal up to 40 mu/m.

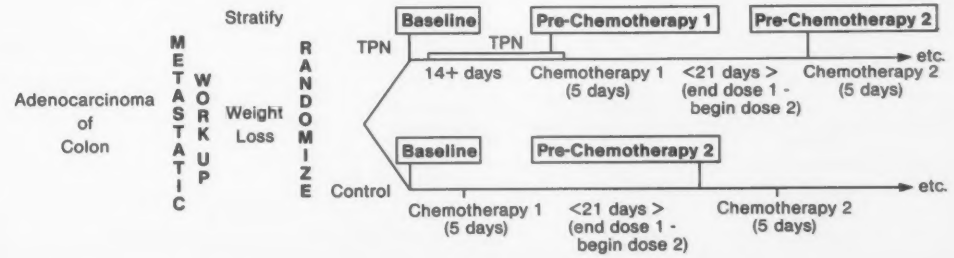

FIGURE 1.—Experimental design.

response in the six randomized patients was brief (6-8 weeks). One TPN patient (not randomized because of 24% weight loss), a 60-year-old-man, had complete disappearance of multiple lung metastases for 3+ years.

5. *Tumor growth and tumor marker changes during TPN.*—No unusual increases in tumor growth were noted clinically during TPN. Median CEA values decreased after 3 weeks (table 4), but ranges were similar in both groups.

6. *Peripheral blood counts.*—Peripheral blood counts showed changes during TPN, but tended to return to baseline 3 weeks after the first course of chemotherapy (table 5). The blood counts for the first two columns of table 5 are based on all patients who had baseline and prechemotherapy 1 measurements; those of the final two columns are based on patients who had prechemotherapy 1 and 2 measurements. For this reason, the mean blood counts for the two columns labeled "Prechemotherapy 1" are not identical. Table 6 exhibits mean changes in the counts of table 5. There are evident increases in platelets and polys and an evident decrease in hematocrit during the TPN period (left half). None of the differences between baseline and prechemotherapy 2 are significant for the TPN group (data not shown). Comparison of blood count changes for the TPN and control groups before and after the first course of chemotherapy shows a signficant difference only for hematocrit.

7. *Zubrod performance status.*—Zubrod performance for the TPN and control groups was similar at baseline, and changed little during TPN and chemotherapy periods (table 7).

8. *Immunological skin tests.*—The number of patients responding to immunological skin tests was too small to draw any useful conclusions (table 8).

9. *Profile of mood states.*—Evidence for a difference between mood states of the TPN and control groups is shown in table 9. The control group shows a greater shift to more negative mood states. This difference is significant ($P < 0.01$) using a Wilcoxon rank sum test.

10. *Nutritional parameters.*—Mean values of four nutritional indexes are contained in table 10. The control group shows no significant changes in these indices during and after the first course of chemotherapy. On the other hand, the TPN group shows some weight gain and lowering of albumin during TPN (table 11) and in the survivors, at least, these changes are maintained through the first course of chemo-

TABLE 4.—CEA values (ng/cc) (Normal < 2.5)

Group		Baseline*	Prechemo 1 for TPN Prechemo 2 for control
TPN	Median	300.0 (16)	169.0 (17)
	Range	1.2-1135.0	0.6-1945.0
Control	Median	205.0 (19)	19.0 (16)
	Range	1.1-1328.0	2.3-1023.0

*Parentheses contain number of patients.

TABLE 5.—Peripheral blood counts*

Group	Count	Baseline	Prechemotherapy 1†	Prechemotherapy 1	Prechemotherapy 2
TPN	HCT (gm%)	35.8 ± 5.0	29.9 ± 5.1 (19)	27.9 ± 3.7	32.2 ± 3.7 (11)
	Platelets (10^3/ml)	299.1 ± 118.1	398.8 ± 172.9 (18)	337.7 ± 117.7	271.4 ± 91.3 (10)
	Polys (%)	60.2 ± 11.0	67.4 ± 9.5 (19)	65.0 ± 9.7	65.7 ± 11.5 (10)
	Wbc (10^3/ml)	7.0 ± 3.0	8.5 ± 5.2 (19)	6.5 ± 3.1	7.0 ± 3.0 (11)
	Lymphs (%)	19.4 ± 9.3	13.9 ± 9.5 (16)	15.2 ± 12.2	21.4 ± 8.4 (9)
		Baseline	Prechemotherapy 2		
Control	HCT (gm%)	36.8 ± 5.3	36.3 ± 5.8 (25)		
	Platelets (10^3/ml)	274.0 ± 141.4	265.2 ± 142.1 (25)		
	Polys (%)	60.7 ± 17.8	63.1 ± 11.6 (23)		
	Wbc (10^3/ml)	8.0 ± 3.0	7.9 ± 3.3 (25)		
	Lymphs (%)	24.5 ± 11.7	25.2 ± 10.8 (23)		

*Expressed as mean ± standard deviation.
†Parentheses contain number of patients.

TABLE 6.—Mean changes in blood counts (data from table 5)

Count	TPN Prechemotherapy 1 − baseline		TPN Prechemotherapy 2 − Prechemotherapy 1		Control Prechemotherapy 2 − baseline	
HCT	−5.9	$P < 0.01$*	4.4	vs	−0.5	$P < 0.01$†
Platelets	99.7	$P < 0.01$	−66.3	vs	−8.8	NS‡
Polys	7.2	$P < 0.05$	0.7	vs	2.4	NS
Wbc	1.5	NS	0.5		0.1	NS
Lymphs	−5.5	NS	6.2		0.7	NS

*Based on paired t-test.
†Based on two-sample t-test.
‡Not significant

TABLE 7.—Summary of Zubrod performance status

Group	Period	0-1	2-4	Total
TPN	Baseline	11 (58%)	8 (42%)	19
	Prechemotherapy 1	8 (44%)	10 (56%)	18
	Prechemotherapy 2	8 (44%)	10 (56%)	18
Control	Baseline	17 (71%)	7 (29%)	24
	Prechemotherapy 2	17 (71%)	7 (29%)	24

TABLE 8.—Immunological skin tests

		Mumps	Monila	SKSD	PPD
TPN	Baseline	1/17*	2/17	1/15	1/17
	Prechemotherapy 1	0/4	0/4	0/4	0/4
	End TPN	0/10	2/10	0/8	1/10
	Prechemotherapy 2	0/2	0/2	0/2	0/2
	Post	1/8	2/8	1/8	0/8
Control	Baseline	1/25	0/25	2/23	0/25
	Prechemotherapy 2	0/14	0/14	0/14	0/14
	Post	0/19	0/19	1/19	2/19

*Entries are expressed as No. positive/No. tested.

TABLE 9.—Mood shifts according to the POMS scale

Group	Period	Increase of 5 or more	Change of less than 5	Decrease of 5 or more	Total
TPN	Baseline-prechemotherapy 1	6 (50%)	4 (33%)	2 (17%)	12
	Prechemotherapy 1-prechemotherapy 2	5 (50%)	3 (20%)	2 (30%)	10
Control	Baseline-prechemotherapy 2	6 (30%)	5 (25%)	9 (45%)	20

TABLE 10.—Nutritional parameters*

Group	Parameter	Baseline	Prechemotherapy 1†	Prechemotherapy 1	Prechemotherapy 2
TPN	Weight (kg)	64.8 ± 11.2	67.7 ± 10.7 (18)	66.1 ± 12.4	66.2 ± 14.0 (9)
	TSF (mm)	11.7 ± 4.8	12.6 ± 5.0 (18)	12.6 ± 5.0	12.2 ± 5.0 (8)
	MAMA (cm^2)	41.0 ± 4.8	42.1 ± 8.8 (18)	41.9 ± 10.2	42.0 ± 12.3 (8)
	Albumin (gm%)	4.0 ± 0.4	3.2 ± 0.5 (10)	3.2 ± 0.6	3.5 ± 0.7 (7)
		Baseline	Prechemotherapy 2		
Control	Weight (kg)	63.6 ± 14.7	63.6 ± 15.9 (25)		
	TSF (mm)	13.7 ± 5.0	13.2 ± 4.8 (24)		
	MAMA (cm^2)	40.2 ± 11.1	41.0 ± 11.5 (24)		
	Albumin (gm%)	4.0 ± 0.6	4.1 ± 0.6 (12)		

*Expressed as mean ± standard deviation.
†Parentheses contain number of patients.

TABLE 11.—Mean changes in nutritional parameters (data from table 10)

Parameter	TPN Prechemotherapy 1–Baseline		TPN Prechemotherapy 2–Prechemotherapy 1		Control Prechemotherapy 2–Baseline	
Δ Weight (kg)	2.9	$P < 0.01$*	0.1	vs	0.0	NS†
Δ TSF (mm)	0.9	NS	-0.4	vs	-0.5	NS
Δ MAMA (cm^2)	1.1	NS	0.1	vs	0.8	NS
Δ Albumin (gm%)	-0.8	$P < 0.01$	0.3	vs	0.1	NS

*Based on paired t-test.
†Based on two-sample t-test; NS = not significant.

therapy. No significant differences are observed in TPN (prechemotherapy 1–2) versus control group (baseline to prechemotherapy 2) changes for these similar periods.

11. *Survival.*—Overall median survival as well as survival in the 0%–6% weight loss stratum was significantly less in the TPN group (table 12).

As of December, 1980, two patients in the TPN group and two in the control group remain alive. The longest survivor (4+ years) is the nonrandomized TPN patient whose lung metastases disappeared with chemotherapy and in whom severe undernutrition was due predominantly to malabsorption/diarrhea secondary to a surgically short gut. TPN in this case was given on two occasions. His course is outlined in figure 2. He was the only patient to receive more than one course of TPN. One control patient with lung metastases remains stable on chemotherapy; the other living control and the TPN patients have progressive disease. All but one have been switched to other chemotherapeutic drugs.

In order to determine variables which might be imbalanced between the TPN and control groups, thereby leading to poorer survival in the TPN group, a log-rank analysis (13) was performed. Since it was found that liver metastases were significantly more numerous in males who received TPN, the sex and liver metastases were used as stratification variables.

When either sex or liver metastases were used to adjust the TPN/control survival comparison, the difference in TPN/control survival was no longer statistically significant. Even after these adjustments, however, no advantage was apparent for the TPN group. A reflection of the effect of liver metastases on survival is shown in table 13. Within the liver metastasis patients, survival remained less in the TPN group; for the group without liver metastases, there is little evidence of a difference. The influence of liver metastases on survival is clear from the medians.

DISCUSSION

The severely undernourished cancer patient has decreased tolerance to antineoplastic therapy, impaired cellular immunity, and reduced or abnormal function of major viscera (14–16). As a result of these or other less well understood influences, survival is decreased with advancing undernutrition in cancer (1).

Colon cancer patients, through gastrointestinal obstruction and surgical resection, liver metastases, or

TABLE 12.—Median survival (days)

Weight loss stratum	TPN	Control	TPN vs control comparisons*
All	79 (20)†	308 (25)	$P = 0.03$
0%-6%	66 (8)	398 (10)	$P = 0.02$
6%-12%	96 (5)	318 (7)	$P = 0.12$
12%-24%	123 (7)	129 (8)	$P = 0.55$

*Using generalized Wilcoxon test (1-sided).
†Using generalized Wilcoxon test (1-sided).

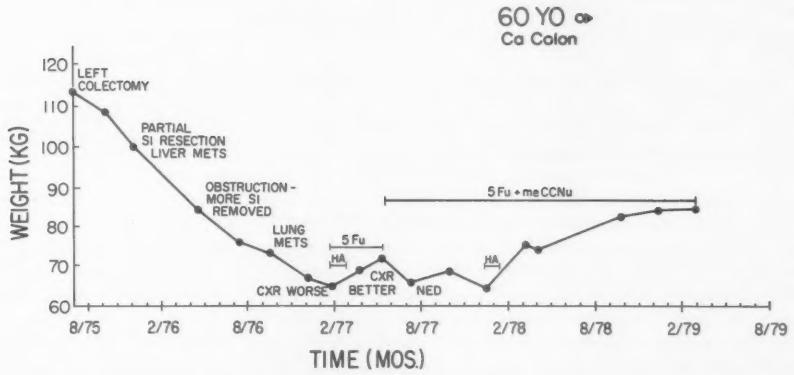

FIGURE 2.—Clinical course for colon cancer patient with malabsorption from surgical resection of small intestine. SI = small intestine; METS = metastases; CXR = chest x-ray; HA = hyperalimentation (total parenteral nutrition); NED = no evident disease.

TABLE 13.—Liver metastases and survival

Metastatic disease	Group	Median survival (days)	Comparison
Liver	TPN	79 (17)	$P = 0.10$*
	Control	171 (17)	
No liver	TPN	> 450 (3)	$P = 0.95$
	Control	547 (8)	
Either	TPN	79 (20)	$P = 0.03$
	Control	308 (25)	

*Based on the generalized Wilcoxon test (one-sided).

additional anorectic-metabolic factors, frequently become undernourished during the course of their disease (17). Since responses to chemotherapy are rare and brief in colon cancer, it is reasonable to attempt nutritional support in hopes of improving treatment. In 1971, Schwartz et al (18) gave central hyperalimentation to three colon cancer patients on 5-FU; two gained weight and one lost. Copeland (14) later reported a greater than expected objective response rate (40%) in 10 colon cancer patients on central hyperalimentation. Gastrointestinal side effects were reduced, septic complications were absent, and tumor growth was not stimulated.

Our randomized study in metastatic colon cancer began in 1977 as part of a larger, multi-institutional investigation involving several diseases and types of treatment with the common aim of comparing TPN versus ad lib feeding. The results of this study confirm that inpatient TPN can be delivered without excessive complications in advanced colon cancer. We are unable

to detect any great effect of TPN on subjective chemotherapy-related symptoms (such symptoms were mild in both groups). No overt stimulation of tumor growth in clinical or biochemical grounds was detected during TPN, but a larger series of patients with longer post-TPN followup is needed to fully answer the question of potential tumor growth enhancement with nutritional repletion. Tumor response rates were low in both the TPN and control categories and were comparable to what is expected with 5-FU and methyl-CCNu in this disease (< 15%) (19). Although Zubrod performance status was affected very little by nutritional route, the TPN group tended to maintain a more positive outlook, perhaps reflecting their perception of more "active" therapy (the TPN).

TPN in the present study caused weight gain, but changes in TSF and MAMA at the end of TPN were minimal. Albumin decreased in the TPN group, suggesting that at least some of the weight gain was added extracellular fluid.

TPN in this series was associated with decreased survival. The randomization procedure resulted in more patients without liver metastases in the control group (based on liver scans), accounting perhaps for some of the survival differences observed. Nevertheless, none of the baseline parameters (including percent of patients with liver metastases) in table 13 were significantly different betwen patient groups. Furthermore, the percentage with abnormal alkaline phosphatase levels was essentially equal in both groups (as were mean levels), which might reflect the comparability of hepatic tumor burden between the two groups more accurately than radioisotope scans which record abnormalities as present or absent without quantification. SGOT levels were likewise similar with mean values within normal levels in the TPN group and only slightly elevated in the control group.

Our experimental design resulted in the TPN patients receiving chemotherapy approximately 2 weeks later than the control (from date of randomization). Since response to chemotherapy was uncommon, it seems unlikely that this time difference had a significant adverse effect on survival in the TPN group.

Notwithstanding the difficulty in obtaining two truly equal groups of cancer patients and the possibility that our TPN group may have been a "less favorable" population, there is no evidence in our study that TPN afforded any benefit in survival duration; survival in this group was still slightly inferior when separate comparision limited to patients with liver metastases was made (table 13).

Thus it appears from our data that short-term TPN as used in this study is not successful in nutritionally repleting most colon cancer patients or in increasing survival. It remains to be proven that longer periods of TPN or repeated courses of TPN would be more effective. Since one patient in our series did quite well, having become severely undernourished after surgical resection of much of his small bowel, it is possible that a subset of patients with similar mechanisms of nutrient loss could be helped by hyperalimentation. In the majority of cancer patients, however, in whom the mechanisms of weight loss remain largely unknown, additional study is needed to refine TPN solutions, delivery times relative to antineoplastic therapy, and duration of repletion to fit specific tumor-host relationships.

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A Prospective Randomized Study of Adjuvant Parenteral Nutrition in the Treatment of Diffuse Lymphoma: Effect on Drug Tolerance

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SUMMARY

Total parenteral nutrition (TPN) has been suggested as a useful addition to chemotherapy of malignant disease in the hope of decreasing drug toxicity and increasing drug tolerance. In this study, 17 of 36 patients given chemotherapy for advanced diffuse lymphoma were randomly selected to receive TPN. The dose of the chemotherapeutic agents to be administered was decreased according to predetermined toxicity guidelines. A comparison of drug dosage in the group receiving TPN and the group receiving standard nutrition is a measure of drug tolerance in these patients. Drug dosage was evaluable in 15 TPN and 18 standard nutrition patients. No difference in tolerance of any specific drug or total drug dose occurred when all patients in both groups were compared. Similar comparisons in subgroups of malnourished patients and responding patients also revealed no difference. A cycle-by-cycle analysis demonstrated no difference in any phase of therapy. The wbc count, platelet count, and albumin level, on the first day of each cycle, the nadir during cycles and the day of nadir were compared in TPN and standard nutrition patients. No differences were found. This study does not suggest improved drug tolerance in lymphoma patients as a result of TPN support. Further controlled studies are needed to determine which groups of cancer patients might benefit from TPN and how these benefits occur.

[Cancer Treat Rep 65 (Suppl 5):129–135, 1981]

It has been suggested that total parenteral nutrition (TPN) given as an adjuvant in aggressive chemotherapy programs might decrease drug toxicity and allow larger quantities of effective drugs to be administered (1). This suggestion has been available for several years and large numbers of patients have been treated on the assumption that it is correct (2,3). However, no controlled studies of drug tolerance in cancer patients undergoing standardized therapy with and without TPN support have been reported.

In the present study of the effect of TPN on patients being treated with intensive combination chemotherapy for advanced diffuse lymphoma, drug doses frequently had to be decreased from proposed protocol levels. Decrease in drug dosage was predetermined according to the drug toxicity encountered. No patient was able to tolerate 100% of the proposed chemotherapy. Comparison of the quantity of drug received by groups of lymphoma patients randomized to receive either TPN or standard nutrition in this study, indicates the effect of TPN on drug tolerance.

METHODS

Thirty-six patients with a tissue confirmed diagnosis of diffuse lymphoma were randomized to receive either TPN or standard nutritional support (fig 1). Patients with stages II, III and, IV as outlined by the Ann Arbor Conference, who had received no therapy other than limited irradiation were accepted (4). Patients were stratified according to histology [diffuse poorly differentiated lymphocytic (DPDL) versus diffuse histiocytic (DHL), diffuse mixed (DML), diffuse undifferentiated (DUL), diffuse lymphoblastic (DL)] and stage [II or III vs IV_{GI} or IV_{marrow} vs IV_{other}].

A three-phase program of chemotherapy with 28-day individual drug cycles was used (fig 1). The induction

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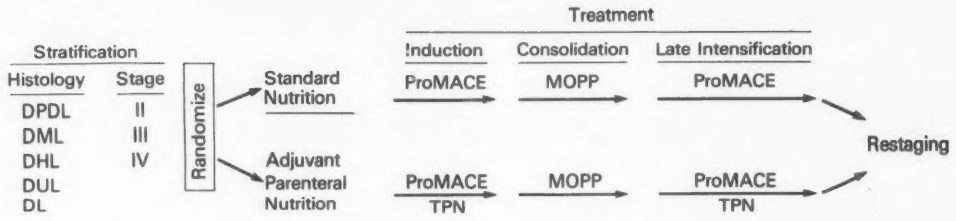

FIGURE 1.—Schema of stratification, randomization, and treatment of advanced stage diffuse lymphoma patients with ProMACE chemotherapy and TPN. Total number of 28-day cycles induction, consolidation, and intensification phase were determined by response to therapy.

phase consisted of multiple cycles of ProMACE (cytoxan 650 mg/m² iv, adriamycin 25 mg/m² iv, and VP-16 120 mg/m² iv on Days 1 and 8; prednisone 60 mg/m² po daily on Days 1–14; and methotrexate 1.5 g/m² on Day 14 with leucovorin rescue). This was followed by a consolidation phase of MOPP (nitrogen mustard 6 mg/m² iv and vincristine 1.4 mg/m² iv on Days 1 and 8 with procarbazine 100 mg/m² po and prednisone 60 mg/m² po daily on Days 1–14. The same number of cycles of MOPP were given as ProMACE in the induction phase. The consolidation phase was followed by a late intensification phase of ProMACE with the number of cycles the same as the induction and consolidation phases but with an additional 28 days between cycles.

The number of cycles in the ProMACE induction phase was determined by tumor response. ProMACE cycles were given until the rate of tumor response decreased or until one cycle after achieving a complete clinical remission. Patients who stopped responding to ProMACE or demonstrated progressive tumor growth were switched to MOPP and did not receive further ProMACE therapy.

Patients randomized to receive TPN were admitted to the hospital the day before each ProMACE cycle (induction and late intensification phases) and had a superior vena cava catheter placed via a percutaneous subclavian or internal jugular puncture. Strict aseptic technique was utilized. A basic TPN solution consisting of 500 ml Freamine II (McGaw Laboratories, Glendale, CA) and 500 ml of 50% dextrose with additional quantities of sodium, potassium, chloride, magnesium, calcium, and phosphate was used. Five ml of a vitamin B-complex solution with vitamin C (Bejex, Abbott Laboratories, Chicago, IL); one ml of a trace metal solution with zinc 5.00 mg/ml, copper 1.43 mg/ml, chromium 0.02 mg/ml and iodine 0.06 mg/ml; and of folic acid 1.0 mg were added to one bottle of TPN solution daily. Five ml of a vitamin A, D, and E solution (MVI concentrate, USV Laboratories, Tuckahoe, NY) was added to one bottle of solution on 2 days each week.

Infusions of the TPN solution were started as soon as radiologic confirmation of correct catheter placement was obtained. Initial rates were 50 ml/hr which were advanced to 125 ml/hr over 24 hours. This rate of infusion was maintained over the first 14 days of all ProMACE cycles. No TPN support was given during MOPP therapy in the consolidation phase. Patients randomized to standard nutrition received all chemotherapy except the high-dose methotrexate during outpatient visits and received no specific dietary therapy.

No data are included in this analysis from patients who were not receiving their planned nutritional program at the time of drug therapy. Data from two patients randomized to TPN were inevaluable and were eliminated because TPN was stopped during the initial cycle as a result of a complication (subclavian vein thrombosis and renal failure) and never reinstituted. Data from one standard nutrition patient were not evaluated because TPN was instituted during the first cycle for severe nutritional debility. Data from MOPP cycles were analyzed only if the patient had received the complete nutritional support required by the protocol during the ProMACE induction phase. Any effect from these exclusions would bias results in favor of the TPN group.

Drug tolerance between TPN and standard nutrition patients using all cycles was first compared using all eligible patients. It was then compared using subgroups selected on the basis of initial nutritional status and on the basis of response to therapy. A malnourished group was defined as having either a weight loss of > 6% of stated pre-illness weight, or serum albumin of 3.6 g/100 ml or less, or both. Patients responding to chemotherapy were defined as those completing the induction phase of ProMACE, achieving complete remission, progressing to MOPP, and remaining disease-free. Analysis of the correlation between initial nutritional status and response to therapy is included. The drug tolerance data between TPN and standard nutrition using all eligible patients was also compared on a cycle-by-cycle basis.

All patients were seen on Days 1, 8, and 14 of ProMACE cycles, and on Days 1 and 8 of MOPP cycles. Nutritional status and drug toxicity were monitored at these times including the sampling of blood for wbc counts, platelet counts, and serum albumin levels. Additional laboratory determinations were performed as indicated by individual patient problems. All available data are included in the analysis of these factors.

Drug dosages were modified from the above 100% levels at the time of each drug administration. One hundred percent of all drugs were given for wbc counts above 4000 cells/mm³, platelet counts above 100,000 cells/mm³, and acceptable general health status. Lesser quantities of the drug were given when blood counts fell below these levels, according to the predetermined schedule (table 1a, b).

TABLE 1a.—Criteria for drug dosage modification*

PROMACE	
Wbc	
Greater than 4000/mm³	100% of all drugs
3000 - 4000	100% MTX 75% CYC, ADR, VP-16
2000 - 3000	100% P, MTX 75% VP-16 50% CYC, ADR
0 - 2000	100% P, 50% MTX, VP-16, 0% CYC, ADR
Platelets	
Greater than 100,000/mm³	100% of all drugs
50,000 - 100,000	100% P, 50% MTX, VP-16 25% CYC, ADR
0 - 50,000	100% P 50% MTX 0% CYC, ADR, VP-16

*P = prednisone; MTX = methotrexate; CYC = cyclophosphamide; ADR = adriamycin.

TABLE 1b.—Criteria for drug dosage modification*

MOPP	
Wbc	
Greater than 4000/mm³	100% of all drugs
3000 - 4000	100% P, VCR 75% PRO, NM
2000 - 3000	100% P, VCR 50% PRO, NM
1000 - 2000	100% P, 50% VRC 25% PRO, NM
0 - 1000	0% all drugs
Platelets	
Greater than 100,000/mm³	100% of all drugs
50,000 - 100,000	100% P, VCR 25% PRO, NM
0 - 50,000	100% P, VCR 0% PRO, NM

*P = prednisone; VCR = vincristine; PRO = procarbazine; NM = nitrogen mustard.

Drug tolerance in TPN and standard nutrition groups was compared by first expressing the drug dose administered as a percentage of the planned protocol dosage. As these percentages are not normally distributed, but trail off from the 100% dose, the median and lower quartile percentages of each drug were calculated for TPN and standard nutrition groups. Drug tolerance in the TPN and standard nutrition groups was statistically compared using the Wilcoxon rank-sum test for the percent of planned dose for each drug separately and all drugs combined.

For each patient the Day 1 values of wbc count, platelet count, and albumin level were averaged over all cycles. The TPN group and standard nutrition group were compared with regard to average Day 1 levels for each of these three parameters by the Wilcoxon rank-sum test. This was also done for nadir values and the day of nadir. All significance tests are of the two-sided type.

RESULTS

Fifteen TPN patients had 43 cycles of ProMACE therapy and 9 cycles of MOPP therapy availble for evaluation (table 2). Eighteen standard nutrition pa-

TABLE 2.—Clinical characteristics of diffuse lymphoma in patients randomized to TPN or standard nutrition

	TPN	Standard nutrition
Total number randomized	17	19
Number with complete nutritional cycle	15	18
Cycles of therapy (ProMACE cycles)	52 (43)	84 (61)
Mean age (Yr ± SEM)	36.3 ± 4.5	47.6 ± 3.1
Stages		
II	3	2
III	3	2
IV	11	15
Histology*		
DPDL	—	1
DHL	14	14
DML	—	4
DUL	2	0
DL	1	—

*See text for definition.

tients had 61 ProMACE cycles and 23 MOPP cycles of therapy for evaluation. The age, stage, and histologic distributions were similar for the TPN and standard nutrition groups (table 2). Twelve of 13 patients (92%) considered adequately nourished at the initiation of therapy responded with a complete remission, while only 9 of 20 malnourished patients (45%) had a similar response (table 3).

Iv nutritional supplementation administered to the TPN group included 2269 ± 26 kcal/day (mean ± SEM) of nonprotein calories and 15.0 ± 0.2 g/day (mean ± SEM) of nitrogen (table 4). TPN patients were allowed oral diets ad libitum during TPN support and had oral nonprotein caloric intakes of 1188 ± 34 kcal/-day (mean ± SEM) and 6.1 ± 0.2 g/day (mean ± SEM) of nitrogen. Total intake for TPN patients was 3457 kcal/day and 21.1 g/day of nitrogen. The outpatient treatment of the standard nutrition group did not permit similar assessment of nutritional intake.

Comparison of drug dosage administered to 15 TPN-supported patients with that administered to 18 standard nutrition patients revealed no significant difference between the two groups (table 5). There were no differences for any specific drug or all drugs combined. A similar comparison of administered drug dose between 11 TPN supported patients and 9 standard nutrition patients who were malnourished at initiation of treatment demonstrated no difference for any

TABLE 3.—Relation of response to nutritional status at initiation of chemotherapy

Nutritional	Responding	Nonresponding	Total
Nourished patients	12	1	13
Malnourished patients	9	11	20
Total	21	12	33

Contingency table analysis $x^2 = 5.71$, df = 1
$P < 0.02$

TABLE 4.—Daily nutritional intakes of TPN patients during 578 days of iv supplementaton (mean ± SEM)

	Nonprotein calories (kcal/day)	Nitrogen (g/day)
Iv	2269 ± 26	15.0 ± 0.2
Oral	1188 ± 34	6.1 ± 0.2
Total	3457	21.1

TABLE 5.—Percentage of planned drug dose (median and 25th percentile percentage)

	All patients		Malnourished patients		Responding patients	
	TPN	Standard nutrition	TPN	Standard nutrition	TPN	Standard nutrition
(n)	15	18	11	9	9	12
Drugs						
Cytoxan	88.4(70.3)	89.9(79.7)	86.0(57.1)	84.4(70.4)	91.9(85.5)	89.3(79.7)
Adriamycin	87.2(75.6)	90.6(78.7)	84.9(71.6)	84.8(65.9)	87.7(81.0)	89.1(78.9)
VP 16	89.6(84.1)	90.5(83.2)	89.5(82.2)	85.7(69.8)	91.2(85.0)	90.5(83.8)
Methotrexate	86.5(56.6)	79.8(51.6)	75.9(46.0)	51.9(48.5)	95.7(87.8)	79.8(51.6)
Prednisone P*	96.0(90.2)	98.1(90.8)	93.7(89.6)	98.0(89.2)	94.8(89.1)	98.1(95.9)
Prednisone M*†	92.4(61.1)	67.5(65.3)	77.1(61.1)	66.4(65.2)	76.8(61.1)	67.6(65.7)
Procarbazine	87.5(65.7)	84.4(72.8)	80.3(62.5)	82.0(65.7)	88.1(75.8)	83.8(73.1)
Nitrogen mustard	80.6(66.0)	80.2(75.0)	75.8(63.5)	75.5(61.7)	86.1(73.3)	84.1(76.0)
Vincristine	88.2(82.9)	87.8(73.5)	93.1(83.9)	78.0(67.5)	85.8(82.7)	91.6(84.2)
All drugs	87.9(70.8)	84.4(77.9)	86.2(67.8)	81.2(74.2)	88.6(86.5)	84.6(83.2)

*Prednisone P = ProMACE cycle.
†*Prednisone M = MOPP cycle.

specific drug or all drugs (table 5). There were no differences when drug dosages from 9 TPN patients and 12 standard nutrition patients responding to therapy were compared (table 5). The same analysis was performed on the respective groups of nourished patients and nonresponding patients and no difference was found.

The finding that no patient received 100% of drugs specified by the protocol and the distribution of drug dosage for all patients evaluated is illustrated in figure 2. The same analysis of data reported above for all evaluable cycles was also performed on all patients on a cycle-by-cycle basis. No difference between TPN supported patients and standard nutrition patients was evident in any cycle for any single drug or all drugs combined.

The mean Day 1 values for serum albumin levels, wbc, and platelet counts were not different between TPN supported and standard nutrition patients (table 6). Similarly, the mean nadirs of these values were not significantly different, nor were the days on which the nadirs occurred.

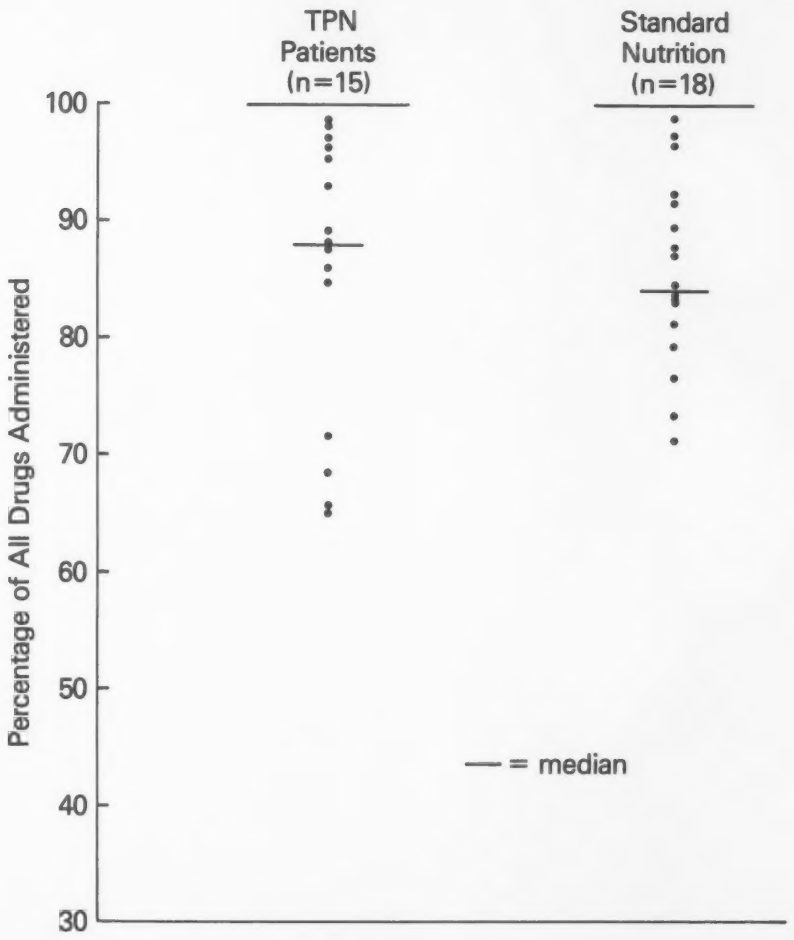

FIGURE 2.—Comparison of the total drug dosage received by 15 TPN patients and 18 standard nutrition patients. No patient received 100% of protocol drug dose.

TABLE 6.—Albumin, wbc, and platelet counts for all patients: Day 1 of cycles, nadir during cycles, day of nadir (Mean ± SEM)

Group	(n)	Day 1	Nadir	Days of nadir
Albumin (g/100 ml)				
TPN	15	3.77 ± 0.15	3.27 ± 0.15	11.1 ± 1.3
Standard nutrition	18	3.74 ± 0.16	3.40 ± 0.14	9.9 ± 1.1
Wbc (x 10^{-3}/mm³)				
TPN	15	7.23 ± 0.62	2.31 ± 0.32	13.5 ± 1.0
Standard nutrition	18	5.80 ± 0.60	2.03 ± 0.30	12.9 ± 0.7
Platelets (x 10^{-3}/mm³)				
TPN	15	331.6 ± 29.4	184.0 ± 22.4	13.0 ± 0.9
Standard nutrition	18	357.2 ± 42.2	168.2 ± 21.1	14.2 ± 0.9

DISCUSSION

The advanced clinical stages of diffuse lymphoma represent major challenges in lymphoma therapy. Results with radiotherapy and single agent chemotherapy have been poor, but recent results with combination chemotherapy suggests that long-term, disease-free survival can be achieved if complete remission can be induced (6–9). The current study was initiated on the premise that the addition of TPN to an aggressive chemotherapy program might allow increased drug tolerance and decreased drug toxicity with subsequent improved survival. This report analyzes drug tolerance. The nutritional effect of the TPN, complications, and long term results of chemotherapy with or without adjuvant TPN have not been addressed.

The better response rate of patients who are in good nutritional condition (92%) compared to patients who have some degree of malnutrition (45%) suggests, as have other studies, that initial nutritional status is a predictor of response. It therefore seems reasonable to add nutritional support to chemotherapy in an effort to increase treatment response rates. This was accomplished in this study with the addition of TPN. The level of support was adequate as 3457 nonprotein kcal/day and 21.1 g/day of nitrogen is in excess of calculated needs, for these patients who rarely had major stress or sepsis (10).

The frequent modification of drug dosage during this study and the failure of any patient to receive 100% of protocol drug dose (fig 2), suggest that comparison of the drug doses received by the two groups is an indicator of drug tolerance.

The failure to find significant increases in any drug dosage or the total drug dosage in the TPN patients when compared to the standard nutrition patients suggests that TPN did not improve drug tolerance. Failure to find increased drug dosage in the malnourished TPN patients indicates that the group most likely to be helped if correction of malnutrition is important did not appear to benefit. Failure to find increased drug dosage in those responding TPN patients indicates that better drug tolerance secondary to TPN was not a factor in their response. The cycle-by-cycle analysis does not suggest an early or late benefit in the TPN group. The independent analysis of wbc counts, platelet counts, and albumin levels indicates that drug toxicity was little affected by the iv nutritional support. These data, therefore, indicate no area of improvement in drug tolerance or decreased toxicity in these lymphoma patients during an aggressive chemotherapy program.

Issell et al (1), in a controlled study, measured the effect of TPN on drug toxicity in a group of patients undergoing chemotherapy for squamous cell carcinoma of the lung. Their data indicate a small improvement in wbc nadir and polymorphonuclear white cell nadir, as well as improved body weight and arm muscle circumferences in the TPN group. Valerio et al (11) measured the effect of TPN on tolerance to abdominal and pelvic irradiation in a controlled study of a group of patients with a variety of different neoplasms. Their data did not suggest increased tolerance to radiation therapy, although a small improvement in nutrition was noted. Most other studies suggesting improved tolerance to antineoplastic therapy are based on inadequately controlled observations (2,3,12,13).

Although this study does not suggest improved drug tolerance or decreased drug toxicity in patients with advanced diffuse lymphoma, it is conceivable that response to therapy and duration of survival might be improved by other mechanisms secondary to an improved nutritional state. Longer followup will be necessary to determine this in these patients. It is also conceivable that patients with different types of malignancies or different types of therapy might have an improved tolerance to therapy as a result of TPN, while the patients with diffuse lymphoma and the chemotherapy of this study did not. This study indicates the need for further controlled studies of TPN in patients with specific malignancies to determine which groups will benefit and how the benefits occur.

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Total Parenteral Nutrition in a Methylcholanthrene-Induced Rat Sarcoma Model

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SUMMARY

Problems with currently available studies of the effects of total parenteral nutrition (TPN) on rat tumor models include: inadequate definition of the natural history of the tumor model; use of nutritional techniques and solutions which have not been proven effective; failure to allow animals to recover from stress of catheterization before starting nutritional manipulation; short-term studies; failure to use sham-operated orally fed control animals; and inadequate evaluation of nutritional result. We have instituted TPN after a 4-day postcatherization recovery period in a defined methylcholanthrene-induced rat sarcoma model. Preliminary results suggest that TPN increases tumor weight without changing tumor composition of water, nitrogen, or fat. TPN also increases carcass fat and water content, but not carcass protein. In tumor-bearing animals, the percentage of energy expended on activity decreases with increasing tumor burden in both TPN and orally fed controls. TPN in these studies appears to support fat stores and stimulate tumor growth.

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Malnutrition in patients being treated for malignant neoplasms is a frequent development. It has been suggested that total parenteral nutrition (TPN) may be beneficial as an adjuvant to conventional forms of cancer therapy (1). This potential benefit has prompted the study of TPN in rat tumor models in an attempt to determine its effects on both the tumor-bearing host and the tumor. Important questions to be answered include the following: (*a*) Will exogenous nutrition benefit the tumor more than the host? (*b*) Does the tumor alter host metabolism in ways that preclude efficient host utilization of exogenous nutrient, eg obligate gluconeogenesis? (*c*) Can special metabolic approaches be devised that will allow metabolic support of the host and be detrimental to the tumor? (*d*) How will TPN interact with other modalities of cancer therapy?

The initial approach to these questions involves determination of the effect of TPN on the natural history of a rat tumor model. For the data to be relevant to human disease it would be useful if the rat developed a malnourished cachetic state similar to that of the human cancer patient, and that TPN be instituted at a time planned to correct this malnourished state. It is essential that the TPN introduced is effective nutritional support comparable to that currently available for human patients. It would then be useful if the model were studied with sensitive indices of nutritional state, such as body composition, radioactive isotope tracers, and calorimetry. The use of appropriate orally fed tumor-bearing (TB) control animals and both orally and TPN supported non-tumor-bearing (NTB) control animals is essential.

The basic approach suggested above has not previously been utilized (table 1) (2–9). In no study has the natural history of the tumor model been well-defined and then TPN instituted during a period of demonstrated malnutrition. Further, the nutritional adequacy of TPN in the rate model has been questioned (6,10). Goodgame et al (10) were able to achieve positive nitrogen balance in growing rats over a 5-day period after catheterization, but found severe fatty infiltration of the liver at that time. Similar findings have been reported by Chang and Silvis (11). Sitren et al (12) abandoned an attempt at a 21-day period of TPN in a rat model because of excessive animal death rates. Cameron et al (4) experienced high death rates in attempts to infuse nutrients iv or intragastrically for 7-day periods. Weight loss in animals being infused

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with presumed adequate iv diets has been commonly reported (11,13). No studies have demonstrated growth, development, positive nitrogen balance, and normal body composition during TPN in a growing rat model. These basic problems all suggest that TPN in the rat is not comparable to TPN in the human patient, and that the TPN-rat model will have to be improved before studies in TB animals are meaningful.

Another problem is the stress response from anesthesia, central venous catheterization, and various harnesses. Birkhahn et al (14) and Goodgame et al (6, 10) have demonstrated weight loss or severe depression of normal weight gain during the first 2–3 days after anesthesia and harnessing in normal orally fed rats. Unfortunately, most studies of TPN in TB rats have begun immediately after catheterization and the results are influenced by both the TPN and the initial stress response to operation. A further problem is that few studies have used sham-operated and harnessed orally fed control animals, and most comparisons of TPN-supported and orally fed animals are therefore invalid (table 1).

The final area of difficulty with current studies concerns the techniques used to evaluate results. Most studies have relied primarily on changes in body and tumor weight, which can be markedly changed by water or fat accumulation (2–7,9). Nitrogen, fluid, and mineral balance studies are more useful, but are frequently falsely positive when stool and urine collections are not complete. In a small animal model, direct carcass analysis of nitrogen, fat, and water can be easily performed, and should be the basic index of nutritional effect (15). If identically treated cohorts are killed and have tumor and carcass composition analyzed at the beginning of the nutritional manipulation, the retention of nutrients by both tumor and host after the manipulation can be independently estimated.

Because of the above difficulties, we have undertaken a series of experiments that address these problems.

METHODS

Definition of Rat Tumor Model

Tumors were produced by injecting 1 x 10^6 viable (by trypan blue exclusion) methylcholanthrene (MCA)-induced sarcoma cells in 0.5 ml solution into the flank of 150-g male Fischer 344 rats (Microbiological Associates, Bethesda, MD). For all of these experiments, a subfascial injection was performed through a skin incision in animals anesthetized with 36 mg/kg of ip pentobarbital. Initial work suggested that the subfascial technique of tumor implantation would produce a precise tumor model. Later independent experiments indicated, however, that subfascial injections provide

TABLE 1.—Comparison of available studies of the effects of TPN on tumor and host

Author (ref no.)	Natural history of tumor defined*	Nutritional adequacy of TPN solution demonstrated†	Duration between catheterization and TPN (days)	Duration of TPN (days)	Orally fed/sham-operated controls	Nutritional monitoring			
						Weight, ▲, albumin‡	Nitrogen balance	Carcass and tumor composition	Other
Steiger et al (2)	–	–	0	10	–/+¶	TW,CW,A	–	–	–
Cameron et al (3,4,7,9)	–	–	0	4–14	+/–	TW,CW	+	Water	–
Stein et al (8)	–	–	0	5	–/+		+	–	^{15}N tracer
Daly et al (5)	–	–	0	7	+/–	TW,CW	–	–	Immune function
Goodgame et al (6)	–	–	0	5	+/+	TW,CW,A	+	Water	DNA H^3-thymidine incorporation
Current study	+	+	4	10	+/+	TW,CW	–	Water, fat, nitrogen	Calorimetry

*Natural history of tumor defined as tumor weight, carcass weight, food intake, and survival from time tumor is implanted until death.

†Adequate TPN solution defined as supporting weight and positive nitrogen balance in adult rats or weight gain and positive nitrogen balance in growing rats over a minimum of 1 wk.

‡TW = tumor weight, CW = carcass weight, A = albumin.

§– = data unavailable.

¶+ = data available.

similar tumor growth characteristics. All NTB control animals were anesthetized and had an incision and subfascial injection of 0.5 ml of sterile saline.

The natural history of the tumor model was defined from the day of tumor transplantation by daily measurement of total body weight, food intake, water intake, tumor size, and duration of survival. After death from tumor, postmortem examinations were performed and tumors were weighed. Tumor weights throughout the growth period were calculated from tumor measurements as suggested by Morrison (16) and carcass weight was calculated by subtracting tumor weight from total body weight.

Both TB and NTB animals were fed ad libitum C-21, a semisynthetic solid diet of demonstrated nutritional adequacy (17).

Improvements in Rat-TPN Model

Long-term (21 days) studies of TPN in growing rats have been performed using modifications of the catheter insertion techniques and the TPN solution described by Goodgame et al (6,10). Catheter insertion technique changes included strict aseptic placement of central venous catheters using autoclaved instruments, wound drapes, sterile gloves, and masks. This insertion technique reduced the incidence of infected catheters from five of six animals to zero of six in a direct comparison with our previous catheterization techniques (18).

Changes in the TPN solution from that described by Goodgame et al included removal of supplemental alanine; addition of vitamins, essential fatty acids, and trace metals; and a decrease in the rate of infusion from 61 ml/day to 40 ml/day of TPN solution plus 5 ml/day of Intralipid (Cutter Laboratories, Berkeley, CA (6,10). The TPN solution utilized an amino acid mixture similar to Freamine II (McGaw Laboratories, Glendale, CA supplemented with arginine (2.4 g/liter), glutamic acid (3.0 g/liter), and asparagine (1.8 g/liter). Dextrose was added to make a 28% solution. Vitamins and minerals were added to supply quantities similar to those recommended for rats by the American Institute of Nutrition in the AIN-76 diet (19). Intralipid in 10-ml quantities was infused on alternate days to prevent fatty acid deficiency. Growing animals infused iv with 40 ml of TPN solution and 5 ml of Intralipid daily demonstrated normal weight gain, positive nitrogen balance, and normal body composition during 21 days of iv feeding.

Nutritional Assessment in TB and NTB Rats

On Day 0, 150-g rats were injected with either tumor cells (TB) or sterile saline (NTB). They were then maintained on C-21 diet until Day 11 when TPN animals had superior vena cava catheterization and orally fed animals underwent a sham operation consisting of internal jugular vein ligation and placement of a flexible shield connected to a swivel identical to that used to protect catheters in TPN animals. Four days were allowed for recovery from operation. On Day 15, TPN animals had oral food removed and were infused with TPN solution and Intralipid at 45 ml/day, while orally fed, sham-operated animals were maintained on an oral diet ad libitum. On Day 25, all animals were killed and complete postmortem examinations performed.

The effects of TPN were evaluated by weighing animals every other day and weighing tumors at the time of death. Carcasses and tumors were then separately homogenized in a blender, lyophylized to determine water content, and the dry material was analyzed for lipid and total nitrogen. Both TB and NTB animals on either TPN or oral diets were also placed in a small animal analytic respiratory calorimeter on Day 15 for measurement of both total energy expenditure and resting energy expenditure (17).

Statistical analysis consisted of one-way analysis of variance with use of a Q test for ranking of mean values when significant differences existed.

RESULTS

Definition of TB Rat Model

In nine animals, subfascial tumor injection killed rats in 31.0 ± 0.7 days (mean ± SEM) with a tumor weight of 66.4 ± 3.3 g (mean ± SEM). Tumors first became palpable on Day 11 and the decrease in host growth and final host weight loss are demonstrated by the carcass weight as shown in figure 1. Diminished food intake started on Day 14 and progressed to almost complete anorexia during Days 27-31 when tumors were large and host weight loss was severe. Postmortem examinations revealed large tumors at flank injection sites, cachectic carcasses, and occasional small pulmonary or other metastases. There was no gross evidence of primary or metastatic tumor causing organ system failure.

Effects of Operation and TPN on TB and NTB Rats

Both catheter placement (TPN rats) and sham operation (orally fed rats) produced similar weight loss from Day 11 to Day 15 in TB and NTB rats (table 2). The mean loss ranged from 13.6 to 21.9 g group. All groups of rats then gained weight after the 4-day recovery period.

Provision of adequate nutrient intake of 47.5 kcal/day by TPN during the period of tumor anorexia resulted in a marked increase in both host and tumor

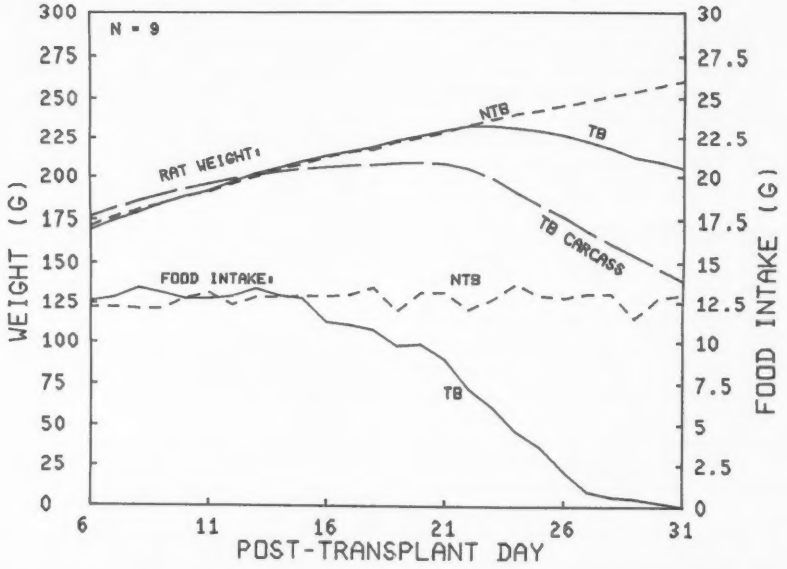

FIGURE 1.—Weight changes and food intake levels in 9 male Fischer 344 rats with subfascial transplantation of MCA-induced sarcoma (TB) and in 9 matched NTB control rats. Mean (± SEM) day of death from tumor was 31.0 ± 0.8. All animals were fed a solid, semisynthetic diet (C-21) ad libitum.

TABLE 2.—Weight changes in TB and NTB Rats
(mean values ± SEM)

	Orally fed-TB rats	TPN-TB rats	Orally fed-NTB rats	TPN NTB rats
	4	4	4	4
Day 0 Total weight	143.6 ± 2.7	146.2 ± 2.3	149.4 ± 4.6	152.4 ± 2.5
Day 11 Total weight	176.2 ± 5.1	175.4 ± 2.8	177.9 ± 3.1	177.5 ± 2.8
Day 15 Total weight	154.3 ± 7.0	161.8 ± 3.0	161.3 ± 3.2	158.5 ± 1.4
Day 25 Total weight	175.3 ± 5.6	215.9* ± 4.6	189.2 ± 4.6	188.3 ± 4.2
Day 25 Tumor weight	29.6 ± 3.1	41.7* ± 2.9		
Day 25 Carcass weight	145.7 ± 5.9	174.2* ± 5.9		
Day 15–25 Caloric intake (k/cal/day)	35.9* ± 3.5	47.5 ± 0.9	52.1 ± 3.2	49.7 ± 1.5

*Different from other mean values in row ($P < 0.05$).

weight when compared with sham-operated, orally fed-TB control animals (table 2). Similar TPN in NTB control animals resulted in weight gains (3.0 g/day) identical to sham-operated, orally fed NTB control animals (table 2). The diminished caloric intake of 39.5 kcal in the orally fed TB animals demonstrates the anorexia caused by the tumor from Day 10 to Day 25 of tumor growth (table 2).

Tumor composition data revealed almost identical percentages of water, protein, and fat concentration in tumors from TPN and orally fed animals (table 3). Carcass composition data in table 3 suggest that the increases in carcass weight observed in TPN-TB animals can be explained by increased carcass water weight and fat weight. Total carcass protein was slightly decreased in the TPN-TB animals when compared to orally fed-TB control animals.

Data from the calorimetry studies suggest little change in resting energy expenditure in TPN supported rats from either orally-fed TB rats or NTB rats (fig 2). Activity energy expenditure (total energy expenditure minus resting energy expenditure), however, progressively declines in both TPN-supported TB rats and orally fed-TB rats as tumor growth progresses.

DISCUSSION

These preliminary results suggest an acceptable approach to the investigation of TPN in the TB rat model. This approach should yield information that may predict results to be expected when TPN techniques are applied to cancer patients.

The MCA rat sarcoma model being studied does resemble human disease in that it causes a severe host cachectic state accompanied by anorexia and leading to death. The mechanisms causing either anorexia or death are not evident from postmortem examination. Although the tumors become quite large, neither they nor occasional small metastases commonly encroach on vital structures. A primary deficiency of this model is that tumors of much greater relative size than are commonly found in human tumor conditions are required to produce the metabolic effect.

The effects of operation in this series of animals indicate an 8%–12% decrease in body weight that occurred primarily during the postoperative days. These data confirm the findings of Goodgame et al (6,10) and Birkhahn et al (14) and indicate the need for appropriate sham operations in orally fed control animals.

Data from TPN support during the period of nutritional impact from tumor and anorexia on the host do not suggest that lean tissue in the animal was supported. The increased carcass weight found in TB-TPN animals initially suggests improvement in the host. Carcass analysis, however, demonstrates that this increased weight consists entirely of water and fat, and that no improvement has occurred in biologically important protein stores. The calorimetry data support this in that both TPN and orally fed TB animals had similar declines in activity energy expenditure at comparable stages of tumor growth.

The increased tumor weight observed in TPN animals and the identical tumor composition indicate that tumor growth was stimulated by the additional nutrient support. This finding contradicts our previous reports of no change in tumor size after 5 days of TPN (6). This finding is consistent with other reports of tumor stimulation by increased nutrient intake (2,3).

The failure to detect improvement in TB rats supported with TPN indicates that the TB host is adversely affected metabolically by the tumor. The area of defect seems to be in protein metabolism, and this might be caused by an obligate gluconeogenic state (20). However, gluconeogenesis from alanine can be suppressed by TPN in cancer-bearing humans under some circumstances (20). The existence of such defects is borne out by well-controlled human clinical studies that have demonstrated little improvement from TPN in cancer patients (21–24). One human study also suggested that normal fat deposition and diminished nitrogen retention occur in cachectic cancer patients

TABLE 3.—Tumor and carcass composition from orally fed- and TPN-TB rats killed on Day 25 (mean values)

Diet	Carcass		Tumor	
	Oral	TPN	Oral	TPN
	3	4	3	4
Total weight (g)	144.7	174.2	32.8	47.5
Water weight (g)	94.3(65)*	107.1(62)	26.6(81)	39.1(82)
Protein (g)†	34.4(24)	32.7(19)	4.9(15)	6.5(14)
Fat (g)	11.7(8)	24.4(14)	0.8(3)	1.1(3)
Total	(97)	(95)	(99)	(99)

*Nos. in parentheses = %.
†Protein (g) = nitrogen (g) x 6.25.

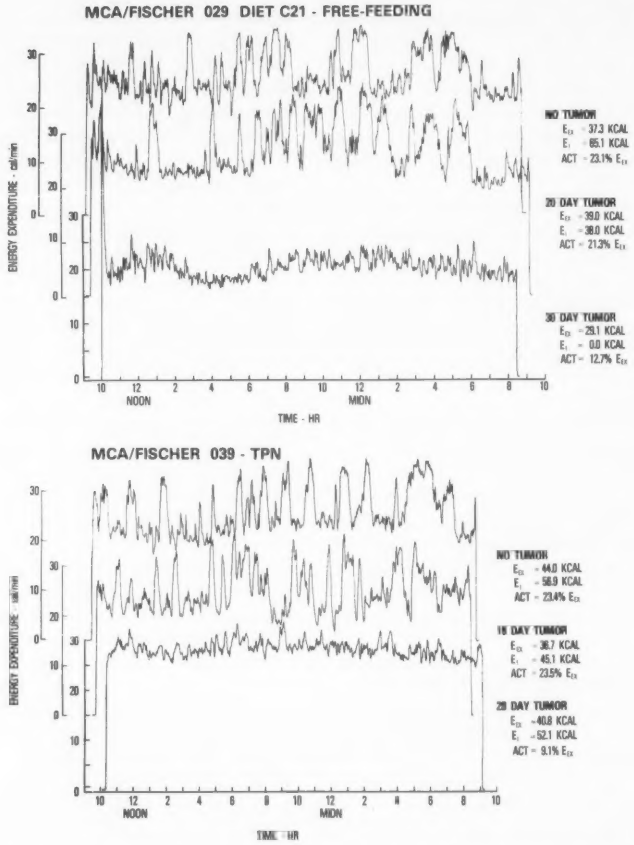

FIGURE 2.—Energy expenditure in free-feeding (top) and TPN-supported (bottom) Fischer 344 rats without tumor and with small and large tumors. E_I = Caloric intake (kcal/24 hr), E_{Ex} = total energy expenditure (kcal/24 hr), ACT = energy expended on motor activity (% E_{Ex}). Activity energy consists of large "spikes" of activity superimposed on baseline of resting energy expenditure. Activity is markedly diminished in the free-feeding rat with a 30-day tumor (E_I = 0.0) and in the TPN rat with a 28-day tumor (E_I = 52.1 kcal).

supported with TPN, which is analagous to the findings of this animal study (25). This suggests that further studies of TPN in TB animal models using the approaches outlined here would be of value both to define metabolic defects in the TB host and to evaluate therapeutic approaches to their correction.

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Role of Intravenous Hyperalimentation as an Adjunct to Intensive Chemotherapy for Small Cell Bronchogenic Carcinoma[1]

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SUMMARY

Forty-nine patients with small cell bronchogenic carcinoma (23 limited and 26 extensive disease) received their first two of three courses of intensive remission induction chemotherapy with (21 patients) or without (28 patients) intravenous hyperalimentation (IVH). The chemotherapy included six remission induction courses with ECHO (epipodophyllotoxin VP-16-213, cyclophosphamide, hydroxydaunorubicin, oncovin), followed by six courses of maintenance with PRIME (procarbazine, ifosfamide, methotrexate). Prophylactic brain irradiation (3000 r/2 weeks) was given to all patients and those with limited disease received chest irradiation (5000 r/5 weeks) at the completion of ECHO. Thus far, all 30 patients who have completed three courses of ECHO have responded with complete (70% CR) or partial (30% PR) remissions. The CR rate was higher for patients receiving IVH (85% vs 59%, $P = 0.25$). Myelosuppression was pronounced and predominantly in the form of neutropenia. Median lowest neutrophil counts were zero during each of the three courses of ECHO and lasted a median of 5 days at levels $\leq 500/mm^3$. Major infections occurred in 21% of courses. The administration of IVH did not ameliorate the hematologic, gastrointestinal, and infectious morbidity of ECHO chemotherapy. However, it resulted in preservation of body weight ($P < 0.01$) and improved skin reactivity to a battery of six skin antigens ($P = 0.03$). The administration of intensive therapy with ECHO ± IVH was well tolerated and resulted in high CR rates in patients with small cell bronchogenic carcinoma. The administration of IVH was most helpful in preventing severe weight loss and augmenting response to a battery of skin antigens. The long term survival effects of these observations are yet to be determined.

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Previous studies have suggested that the administration of IVH as an adjunct to antineoplastic chemotherapy for nonsmall cell lung cancer could be associated with amelioration of hematologic and gastrointestinal toxicities of the chemotherapy (1–3). These observations raised the possibility that under conditions of nutritional support, larger doses of antineoplastic chemotherapy could be administered. Accordingly, we elected to investigate this possibility in patients with small-cell bronchogenic carcinoma (SCBC), a disease known to be responsive to a variety of antineoplastic chemotherapeutic agents and where Cohen et al (4) and others (5) have suggested that complete remission from disease and prolonged survival

are more likely to occur with chemotherapy programs of increased intensity. The preliminary results of such an ongoing study are presented here.

PATIENTS AND METHODS

Patients with SCBC who received no prior chemotherapy were eligible for this study. Patient entry was not restricted because of age, prior chest irradiation, or the presence of brain metastases. Patients were aware of the investigational nature of the study and informed consent was obtained according to institutional policies.

Pretreatment staging investigations included history and physical examination; cbc; SMA-100; urinalysis; serum electrolytes; chest x-rays; bronchoscopy with bronchial brushings, washings, and biopsy; sputum cytology; pulmonary function tests; bone marrow aspiration and biopsy; CAT scan of the brain, and scans of the liver and bone.

Upon completion of staging workup, patients were admitted to the hospital and randomized to receive an initial remission induction treatment with or without IVH. Stratifications were made for sex, disease extent (limited vs extensive), performance status (ambulatory vs nonambulatory), and pretreatment weight loss (<6% vs >6%). The antineoplastic therapy consisted of the sequential administration of two sets of combination chemotherapy, ECHO and PRIME, plus prophylactic whole brain irradiation given to all patients and chest irradiation to patients with limited disease only. ECHO consisted of epipodophyllotoxin VP-16-213, cyclophosphamide, hydroxydaunorubicin, and oncovin. PRIME consisted of procarbazine, ifosfamide and methotrexate. Six courses of ECHO were given first, each at approximately 3-week intervals. The first three courses were given as inpatients and the remaining three as outpatients. Prophylactic whole brain irradiation (3000 R in 10 fractions over 2 weeks) was given concomitantly with the fourth course of ECHO. Chest irradiation (5000 rads in 25 fractions over 5 weeks) was given after completion of the sixth course of ECHO. Thereafter, patients received six courses of outpatient PRIME chemotherapy, each at 3- to 4-week intervals. The dosage and schedule of administration of ECHO and PRIME chemotherapies are shown in table 1. With the exception of VP-16-213, ifosfamide, and procarbazine, all other agents were given iv dissolved in 100 to 200 ml of 5% dextrose solution or normal saline and over a 15- to 30-minute period. VP-16-213 was given iv dissolved in 500 to 1000 ml of normal saline and over a 3- to 4-hour period. Ifosfamide was given iv dissolved in 500 to 1000 ml of 5% dextrose solution or normal saline and over a 2- to 3-hour period. Procarbazine was given orally. During the initial inpatient induction, treatment doses were modified as indicated in table 1, in an effort to achieve an absolute neutropenia $\leq$ 500 and/or thrombocytopenia $\leq$ 50,000/mm^3, respectively, and lasting no more than 5 days. During all phases of the treatment, the doses of chemotherapy were reduced for the development of infectious and/or bleeding complications.

Patients randomized to receive IVH did so during first two out of the three initial courses of ECHO chemotherapy, that is for approximately 6 weeks. Iv hyperalimentation and chemotherapy were started simultaneously. The IVH was administered through a 16-gauge, 20-inch silicone elastomer catheter (Intrasil, Vicra Corp) with an internal volume of 0.4 ml introduced percutaneously in the basilic or cephalic veins of the antecubital fossa and advanced to the superior vena cava. Strict aseptic technique was used for catheter insertion, dressings, and IVH tubing changes were performed 3 times a week. The IVH formula consisted of a standard preparation of 500 ml of 50% glucose and 500 ml of 8.5% amino acid solution plus electrolytes, vitamins, and minerals added daily. Twice weekly, patients received 500 ml of 10% Intralipid. An attempt to deliver 3000 calories iv per day was maintained, in addition to oral nutrition ad lib. Catheter tips were cultured when removed.

Controls and IVH-treated patients underwent several nutritional and immunologic studies prior to and at different points during their therapy. These studies included determinations of body weight changes, nitrogen balance, creatinine-height index,

TABLE 1.—ECHO-PRIME chemotherapy: drugs and dosages

a) ECHO: Dose level No.		VP-16-213 (mg/m^2/D 3-5)	Cytoxan (mg/m^2/D 1)	Adriamycin (mg/m^2/D 1)	Oncovin (mg/D 1 & 8)
	2	100	1000	60	1.5
Initial	1	75	750	50	1.5
Maintenance	-1	50	500	40	1.5

b) PRIME: Dose level No.		Procarbazine (mg/m^2/D 1-10)	Ifosfamide (mg/m^2/D 1-5)	Methotrexate (mg/m^2/D 1)
	2	120	1200	60
Initial	1	100	1000	50
	-1	80	800	40

arm muscle circumference, triceps skin fold measurements, and daily caloric and nitrogen intakes. Also, studies of delayed hypersensitivity reaction with a battery of skin tests (dermatophytin, *Candida*, mumps, varidase, PPD and KLH) as previously described (6) and studies of inflammatory response by the skin window technique (7).

Patients were monitored closely throughout their hospitalization. This included blood pressure determinations during the time of VP-16-213 administration because of the possibility of postural hypotension. Patients had cbcs daily, serum electrolytes 2–3 times weekly, SMA-100 and urinalysis weekly, and chest x-ray examinations prior to each course of chemotherapy or more often if indicated. At the time of discharge, patients' disease was re-evaluated by repeating all pretreatment investigations including bronchoscopy. These investigations were also repeated at the completion of six courses of ECHO and six of PRIME chemotherapy.

The response to chemotherapy was assessed prior to each course of chemotherapy by using standard criteria. To be evaluable for response, patients must have had measurable disease and should have completed at least two courses of ECHO chemotherapy. Patients who died during the administration of the first two courses of chemotherapy were considered early deaths. Even if these patients achieved tumor response, they were not evaluable for response. All patients, however, were evaluable for toxicity and survival analysis. Complete remission consisted of the disappearance of all symptoms and signs of malignancy. Partial remission consisted of a reduction ≥ 50% of the sum of all measurable tumor. Patients who did not achieve a complete or partial remission, as well as those whose disease increased during treatment or those who developed new lesions, were considered progressors. Survival curves were calculated by the method of Kaplan and Meier (8), and tests of differences in survival distributions were based on a generalized Wilcoxon test (9). A chi-square test was utilized to test for differences in response, gastrointestinal toxicities, and infectious complications between control and IVH groups. Other results for control and IVH groups were compared using an unpaired T-test or the Mann-Whitney test.

RESULTS

As of September 30, 1979, 49 patients were entered into this study, 21 in the IVH arm and 28 in the control arm (table 2). Groups were comparable with exception of a slight predominance of patients with extensive disease in the control arm.

At the time of this analysis, 30 patients had completed their first three courses of ECHO chemotherapy and were considered evaluable for tumor response (table 3). The 19 inevaluable patients included 3 with extensive mediastinal disease but not measurable disease, 8 who had not completed their initial inpatient induction treatment, 7 who died within the first 2 weeks of treatment, and 1 patient who died at the beginning of the second course of chemotherapy. All evaluable patients have responded to chemotherapy with a complete or partial remission. The overall complete remission rate was 70%, being slightly greater in patients receiving IVH, 85% versus 59% ($P = 0.25$). Complete remission rate was just as high in patients with limited and extensive disease (10 of 14, 71% vs 11 of 16, 69%, respectively). The administration of IVH was associated with a greater, though not significant, complete remission rate in patients with limited disease (7 of 7, 100% vs 3 of 7, 43%, respectively, $P = 0.07$) and ambulatory performancy status (9 of 10, 90% vs 8 of 13, 57%, respectively, $P = 0.19$).

The myelosuppressive toxicity during the first three courses of ECHO chemotherapy in relation to the administration of IVH is summarized in table 4. The

TABLE 2.—ECHO-PRIME ± IVH: patient characteristics

	IVH	No IVH
Entered	21	28
Sex: Female	6	7
Male	15	21
Age: Median	58 yrs	58 yrs
Range	37-68 yrs	46-79 yrs
Performance status:		
Ambulatory	14	19
Non-ambulatory	7	9
Disease extent:		
Limited	11	12
Extensive	10	16
Special problems:		
Superior vena cava compression	4	2
Brain metastasis	4	3
SIADH*	1	3

*Syndrome of inappropriate antidiuretic hormone.

TABLE 3.—ECHO-PRIME ±IVH: results

	IVH	No IVH
Entered	21	28
Inevaluable:	8	11
Unmeasurable	2	1
Too early	2	6
Early death	4	4
Evaluable	13	17
Remission:		
Overall	13 (100%)	17 (100%)
Complete	11 (85%)*	10 (59%)*
Partial	2 (15%)	7 (41%)

*$P = 0.25$.

TABLE 4.—Myelosuppressive toxicity during remission induction with ECHO ± IVH

Course no.	Counts x mm³	IVH	No IVH
1	Median lowest neutrophils	0(21)*	0(25)*
	Median days ≤ 1000	8	9
	Median days ≤ 500	5	4
	Median lowest platelets	108,000	97,000
	Median days ≤ 100,000	0	0
2	Median lowest neutrophils	0.1(18)*	0(21)*
	Median days ≤ 1000	8	8
	Median days ≤ 500	5	5
	Median lowest platelets	109,000	114,000
	Median days ≤ 100,000	0	0
3	Median lowest neutrophils	0.25(16)*	0(20)*
	Median days ≤ 1000	4	7
	Median days ≤ 500	1	4.5
	Median lowest platelets	121,000	119,000
	Median days ≤ 100,000	0	0

*No. evaluable courses.

degree and duration of myelosuppression were profound and not significantly different between both treatment arms, with exception of a slight advantage of the IVH treated patients during the third course of chemotherapy. Myelosuppression was predominantly in the form of neutropenia with median nadir counts approximating zero and lasting for approximately 5 days at levels ≤ 500/mm³. These results did not appear influenced by modifications in drug doses required during the study. Sixty percent of all courses of chemotherapy administered during the inpatient induction part of the study did not required dosage modifications. Dosage escalations were conducted in 20% of the IVH treated patients as opposed to 25% of the control group, whereas dosage reductions were needed in 14% of the IVH group as opposed to 15% of the controls.

A summary of the infectious complications observed during this study is presented in table 5. It includes the overall frequency of febrile episodes, fevers of unknown origin (FUOs), episodes of documented infections, fatal infections as well as that of the infecting organisms. Just under one third of treatment courses of each study arm were associated with newly developed febrile episodes. Episodes of documented infections were slightly more common in the IVH-treated arm (27% vs 14%), although this difference did not reach statistical significance ($P = 0.09$) Pneumonia alone or in combination with septicemia was the most common infection and it appeared more common in the IVH treated patients. With the exception of six episodes of pneumonia in which the infecting organisms could not be identified, the most common causative organisms were gram-negative bacilli (58%). Of interest, five out of six infections caused by *Pseudomonas* occurred in the IVH group. The development of infectious complications could not be related to local catheter complications. Of 33 catheters inserted into

TABLE 5.—Infectious complications related to the use of IVH

	IVH	No IVH
Evaluable courses	59	72
Febrile episodes:	18 (31%)	17 (24%)
FUO	2 (3%)	7 (10%)
Infections	16 (27%)*	10 (14%)*
Fatal infections	3 (5%)	3) 4%)
Infections		
Pneumonia	8	2
Pneumonia & septicemia	4	1
Septicemia	-	2
UTI	4	3
Mucositis	-	2
Organisms		
Unknown	4	2
Pseudomonas sp	5	1
Klebsiella-Enterobacter-Serratia	3	1
E coli	1	2
Proteus sp	1	-
Beta streptococcus	-	1
Candida sp	3	2
Nocardia sp	1	-
S epidermidis	1	1
S aureus	1	-

*$P = 0.09$.

28 patients, just over one-third were associated with the development of local phlebitis and eight (24%) needed to be removed because of severity of the phlebitis. In three instances, patients developed subclavian thrombosis and required removal of the catheter. All catheter tips were cultured upon removal and yielded no growth. Among other toxicities associated with the administration of IVH, we observed a 33% incidence of hyperglycemia requiring insulin supplementation and a 14% incidence of clinically detectable pulmonary congestion due to fluid overload.

The effects of nutritional support on the gastrointestinal toxicities associated with the administration of chemotherapy as well as the relationship between caloric intake and weight changes during the first two courses of chemotherapy are summarized in table 6. Vomiting and mucositis were common in both treatment arms, although usually mild. The percent of hospital days spent with mucositis was higher in the IVH group (11% vs 6%) and reached high statistical significance ($P < 0.01$). The mean daily caloric intake of the IVH treated patients was almost twice as high as that of the control patients (3360 vs 1677 kilocalories). Approximately 80% of the total caloric intake of the IVH group was due to IVH. This difference was not surprisingly reflected in the 6% median weight gain of the IVH patients over their pretreatment weight as opposed to a net loss of 5% for the controls ($P < 0.01$). Preliminary analysis would indicate that weight gain in these patients correlated well with improvements in nitrogen balance and lean body mass.

TABLE 6.—Effects of intravenous hyperalimentation on gastrointestinal toxicities of chemotherapy, caloric intake, and weight changes during therapy

	IVH	No IVH	P*
Patients evaluated	21	28	
Patients with vomiting	16(76%)	15(54%)	NS
Patients with mucositis	9(43%)	10(36%)	NS
Days of hospitalization	1113	1349	
Days with vomiting	84(8%)	78(6%)	0.09
Days with mucositis	118(11%)	81(6%)	<0.01
Mean daily kcal			
Total	3360	1677	<0.01
Due to IVH	2589	—	
Median pretherapy weight in pounds (range)	148.5(94-207)	151.5(110-253)	NS
Median post-therapy weight change	+6%(+8 lb)	-5%(-8 lb)	.01

*NS = not significant.

Results of studies of delayed hypersensitivity reaction with a battery of six skin antigens favored the IVH group. Considering an area of induration ≥ 100/mm² at 24 to 48 hours as a positive test, a third of the patients in each treatment arm had positive pretherapy skin tests (38% vs 337, $P = 0.66$). Prior to the second and third courses of chemotherapy, however, it became apparent that patients maintained on IVH had a higher rate of skin test positivity (51% vs 32% and 67% vs 46%, respectively, $P = 0.03$).

Five patients have thus far relapsed, three IVH treated patients and two controls. Relapses occurred at 20, 29, and 42 weeks from the point of remission in the IVH group and at 20 and 26 weeks in the controls. Four of the five relapsing patients recurred in the central nervous system (one in the brain and three in the cord). However, three of these patients already had brain metastases at presentation. Fourteen (29%) patients entered in this study died, 5 (24%) in the IVH group and 9 (32%) in the controls ($P = 0.7$). Eleven (58%) deaths occurred in patients presenting with extensive disease (4 IVH and 7 controls). At the time of death, there were five patients in remission (two complete and three partial) and two with progressive disease. Infection was the most common immediate cause of death (seven patients, 50%). Other causes were: disease progression (two) bleeding (two) myocardial infarction (two), and unknown (one). The treatment alone could be held responsible for the death of three patients (two IVH and one on IVH), whereas in four other patients (two in each group) death was most likely related to massive multiorgan replacement by tumor plus added chemotherapy toxicity. A graphic representation of the survival of all patients entered into each arm of the study is shown in figure 1. Both curves contain a significant degree of artifact because of the number of patients who are still at early stages of their followup. The median survival for both groups has not yet been reached, and there appears to exist certain divergence of the curves at 20 weeks of followup with an advantage for the IVH group. This difference, however, is not statistically significant ($P = 0.38$).

DISCUSSION

This ongoing study suggests that the administration of intensive antineoplastic chemotherapy as induction treatment for patients with SCBC is capable of producing high complete remission rates in patients with both limited and extensive disease. This approach appears limited, however, by significant infectious morbidity occurring during periods of severe neutropenia. Similar problems have previously been described in patients with SCBC receiving an intensive remission induction treatment consisting of simultaneous chemotherapy and radiation therapy (5). Accordingly, it appears justifiable to investigate prophylactic measures aimed at the prevention of infectious complications or at shortening the periods of severe neutropenia during treatment programs of great intensity in these patients. Such studies which include the evaluation of prophylactic antimicrobial antibiotics, protected environment-prophylactic antibiotic units, and autologous bone marrow transplantation are now in progress at our institution.

The administration of nutritional support in the form of IVH as an adjunct to intensive chemotherapy in this study appeared most helpful in maintaining or improving patients' pretreatment weight as well as improving their delayed hypersensitivity reaction as measured by a battery of skin test antigens. The beneficial effects of IVH in these areas have previously been reported (10-2). In contrast to previous reports (1-3), however, we did not observe in this study any protective effect of nutritional support against the gastrointestinal, hematologic, and infectious morbidity of the chemotherapy given. In fact, we encountered an increased frequency of mucositis and infectious morbidity in the IVH treated group. The apparent discrepancy of these observations could in part be related to the contribution of different variables such as underlying disease, type and intensity of the antineoplastic treatment, type, duration, and timing of the nutritional support in relation to the therapy, etc. Complete tumor remission which is so closely related to prolonged survivorship in SCBC was only minimally improved by the administration of IVH in this study. Likewise, the survival advantages for these patients is thus far not significant.

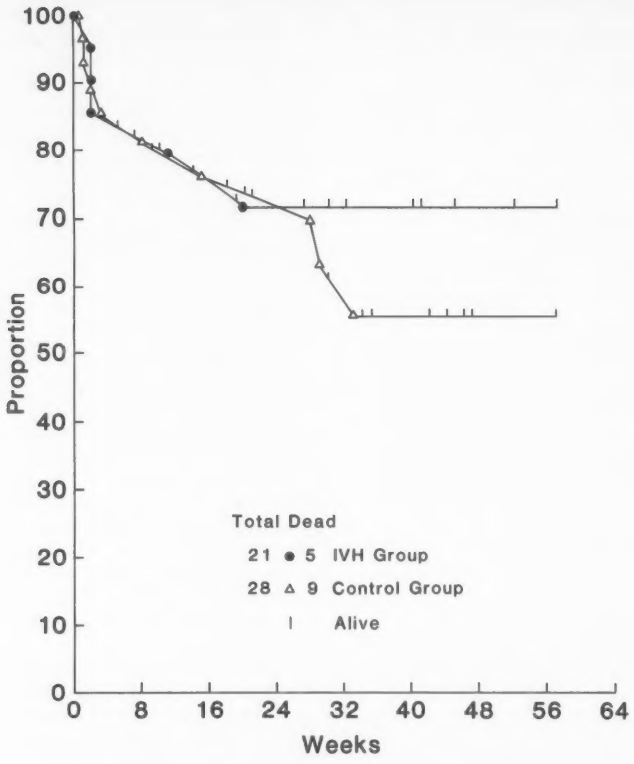

FIGURE 1.—Survival of patients with small cell lung cancer related to the administration of intravenous hyeralimentation.

The administration of nutritional support in the form of IVH during intensive antineoplastic chemotherapy for SCBC is safe and more helpful in preventing severe weight loss and improving patients' delayed hypersensitivity reaction. Thus far, this study has not shown evidence that this administration of IVH could ameliorate chemotherapy-induced toxicities or improve patients' response and survival.

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Parenteral Intravenous Nutrition (PIVN) as an Adjunct to Chemotherapy in Small Cell Anaplastic Lung Carcinoma[1]

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SUMMARY

A randomized trial was initiated to compare the effects of PIVN-associated chemotherapy (adriamycin, vincristine, VP16-213 and cyclophosphamide) versus a chemotherapy control group in patients with small-cell lung neoplasias. The results obtained are preliminary. The test group included ten patients whereas nine were followed in the control group. PIVN was scheduled each day the patient underwent chemotherapy. Each patient received 1550 kcal/day, which included 10% glucose, 20% lipids, and amino acids which may or may not be mixed in the same infusion bottle. The results show three PIVN patients presently in complete remission at the end of three courses of treatment compared to two over the same time period in the chemotherapy control group. Of all patients who can be evaluated at this time, five out of six PIVN patients are in complete remission compared to four out of five in the control group. There was no significant difference in either general health or side effects, such as nausea and vomiting. The median length of time for which a low white cell or platelet count was noted was the same for both groups.

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The treatment of cancers by chemotherapy, in particular solid tumors, is becoming more routine due to the availability of new drugs as well as the increasingly efficacious combinations of drugs as a result of pharmacological progress. Nevertheless, there are still difficulties associated with the toxicity of the drugs employed and poor results for recommended doses of some products. Parenteral hyperalimentation is a relatively new, important development that numerous authors have suggested may find a role in the general treatment of cancer possibly reducing drug toxicity (1-5). Other studies have suggested that this therapy can, under certain conditions, stimulate tumor growth (6), while still other have rendered an opposing viewpoint suggesting that it promotes higher patient tolerance leading to a more intense therapy (1-5). Nevertheless, up to now, no clearcut randomized trial (1) has been published to confirm or deny these hypotheses. It is further pointed out that the techniques involved are difficult to manage.

These considerations led us into a French-American agreement in which we initiated a randomized trial of the bronchogenic chemosensitive small-cell carcinoma in order to evaluate the possibility that PIVN could play a protective role against toxicities arising from intensive chemotherapy and/or that it could ameliorate patient response to treatment. In this paper we present our results which are, admittedly still preliminary.

PATIENTS AND METHODS

This randomized trial was performed with patients demonstrating histological small-cell lung carcinoma. All patients presented with a measurable tumor. We did not exclude patients who were previously treated by radiotherapy. After selection, patients were randomly assigned either to the PIVN-chemotherapy or chemotherapy control group: (*a*) parenteral nutrition group: 6 evaluated patients out of 10; (*b*) no parenteral nutrition group: 5 evaluated patients out of 9. All patients were evaluated both before and after each chemotherapeutic cycle. The parameters chosen were the following: performance status, weight, blood pro-

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file; carcinoembryonic antigen; α-fetoprotein; inflammatory proteins (C-reactive protein, haptoglobin, orosomucoid, lysozyme, α-2-macroglobulin); delayed hypersensitivity skin tests; circulating immune complexes; immunoglobulins; and liver function. Before each treatment and after every three treatments, each patient underwent fibroscopic examination (with histological biopsies taken), bone marrow studies, and bone, brain, and liver scintiscans. If brain scintiscans were not done, an electoencephalogram was ordered. All patients had an electrocardiogram before each treatment.

PIVN was administered over an 8-hour period for each chemotherapeutic cycle beginning with the day of chemotherapy. PIVN was repeated with each chemotherapy treatment. This alimentation contained 1550 kcal per day (either mixed in a single iv bottle or administered individually) and included 1000 ml of 10% glucose, 500 ml of 20% lipids, and 500 ml of protinutril. The infusion was introduced into a peripheral vein and, in most cases, did not necessitate catheterization of the inferior or superior vena cava. PIVN lasted 8 hours.

Chemotherapeutic agents were administered through the same iv access as PIVN. Three courses of intensive induction chemotherapy (ECHO program) were administered followed by a 30 grays cranial irradiation for 2 weeks and a maintenance period of three chemotherapy cycles (ECHO PRIME). If the patient demonstrated complete remission, a final 12 courses of PRIME program were given. The three-course chemotherapy ECHO program included the following drugs: on Day 1, adriamycin at 50 mg/m², 70 mg/m² or 75 mg/m²; vincristine at 1.5 mg and cyclophosphamide at 0.75 g/m², 1 g/m² or 1.2 g/m²; VP 16-213 was given on Days 3, 4, 5, and 6 at 75 mg/m², 100 mg/m² or 120 mg/m²; vincristine was given on Day 8 (1.5 mg). The Day 1 maintenance period (ECHO-PRIME) consisted of adriamycin (40 mg/m²), cyclophosphamide (500 mg/m²) and vincristine (1.5 mg on Days 3, 4 and 5, VP 16-213 was 50 mg/m²; on Day 8, 1.5 mg of vincristine was administered. The PRIME program, lasting from Day 1 to Day 10, consisted of procarbazine (100 mg/m² po, from Day 1 to 5, iphosphamide iv (1000 mg/m²) and methotrexate iv on Day 1 (50 mg/m²). PIVN was administered only during ECHO and ECHO-PRIME programs.

The patients were regularly given a complete physical examination with x-ray of the lungs, pulmonary fibroscopy (including biopsy), and scintiscans every 3 courses of chemotherapy. The criteria for judging patient response were the following: complete remission corresponded to complete disappearance of all clinical, radiograhic, and laboratory manifestations of the tumor. Partial remission was defined as a decrease ≥ 50% of the product of the two perpendicular diameters of the lesion without the appearance of any new lesions. The disease was considered to evolve if all lesions measured increased ≥ 25% or if new lesions appeared.

RESULTS

Patient characteristics are similar in the two groups (table 1). Six of ten patients treated by PIVN-chemotherapy were evaluated, and five are presently in complete remission. One patient did not respond to therapy and eventually died. In the control chemotherapy group (table 2) four of the five patients evaluated (nine patients total) are in complete remission. One case where the disease continued to evolve resulted in death. In the first group, three patients demonstrated complete remission after three high-dose treatments, whereas only two were noted in the control group at the same drug concentrations. Similar, but retarded, results were obtained for patients who could not receive maximum drug doses. One patient presented with medullary infiltration that totally disappeared after chemotherapy.

Effects on the weight.—Evaluation of patient weight (fig 1) showed that their weight varied between 0 and ± 3 kg. Again, there was no significant difference between the two groups either in weight gain or loss. Note that both patients who did not respond to treatment demonstrated a weight loss of 2 kg per treatment cycle.

Evaluation of digestive tract toxicity.—The PIVN group had one patient more than the control group who experienced nausea and vomiting during chemo-

Table 1.—Patient characteristics

	Parenteral nutrition	No parenteral nutrition
Sex: female	1	0
male	9	9
Age: Median	52	54
(years) Range	40-64	42-66
Performance status		
Ambulatory	8	9
Nonambulatory	2	0

TABLE 2.—Preliminary results after ECHO program

	No. of patients	No. of ECHO courses level a	b	c	1	2	3	4	5
	3			3	3				
A	1		3	1	1				
	1		6		1				
	1			3					1
	2			3	2				
B	1		3	1	1				
	1	4	3		1				
	1		3						1

A=parenteral nutrition; B=no parenteral nutrition.
1=complete remission; 2=remission 50%;
3=remission 50%; 4=stabilization; 5=progression.
a=low dose, b=middle dose; c=high dose

therapy (table 3). This difference is not significant, considering that the PIVN group contained six patients compared to five in the non-PIVN group.

Evaluation of marrow toxicity.—Evaluation of the myelosuppressive effects of chemotherapy (table 4) showed that there was no significant difference in white cell levels, even though the minimal value noted for the PIVN group was lower than the non-PIVN group. Platelet changes only became evident after the third chemotherapy course, in contrast to low wbc counts that were observed after the second. Nevertheless, there is no difference in myelosuppression for the two groups when the median number of myelosuppressive days is anlayzed (table 5). The recuperation time for wbc to attain or surpass 1000/mm³ or for platelets to reach 100,000/mm³ was identical for the two populations. In one patient white cells dropped to less than 200/mm³ during 3 weeks and platelets to less than 45,000/mm³ in a second subject. In spite of these extreme cases, we observed no major infections nor hemorrhages necessitating platelet infusion.

Complications.—There were no major complications related to PIVN therapy, partly due to the fact that we did not employ an indwelling catheter. There were no complications due to sepsis, no incidence of phlebitis, and no complications linked to the administration of lipds. Paresthesia associated with the administration of vincristine did not require cessation of treatment.

TABLE 3.—Gastrointestinal toxicity

	Parenteral nutrition	No parenteral nutrition
No. patients	6	5
Patients with vomiting	4	3
Patients with nausea	3	3

TABLE 4.—Effects of parenteral nutrition on chemotherapy-induced myelosuppression

	Parenteral nutrition	No parenteral nutrition
No. patients/no. courses	6/16	5/17
Nadir median wbc		
1st course	600	750
2nd course	1230	900
3rd course	1071	840
Nadir median platelets x 10^3		
1st course	100	109
2nd course	118	121
3rd course	124	89.3

TABLE 5.—Median duration (days of myelosuppression)

	Parenteral nutrition	No parenteral nutrition
Wbc ≤ 1000/mm³		
1st course	8	8
2nd course	8	10
3rd course	2	4
Platelets ≤ 100,000/mm³		
1st course	12	8
2nd course	7	0
3rd course	0	0

The patient was subsequently treated with three 5-mg injections of folinate. Constipation was noted in 5 cases.

DISCUSSION

The present results are still too preliminary and the number of patients too limited to draw definite conclusions. Nevertheless, one can note the remarkable effect

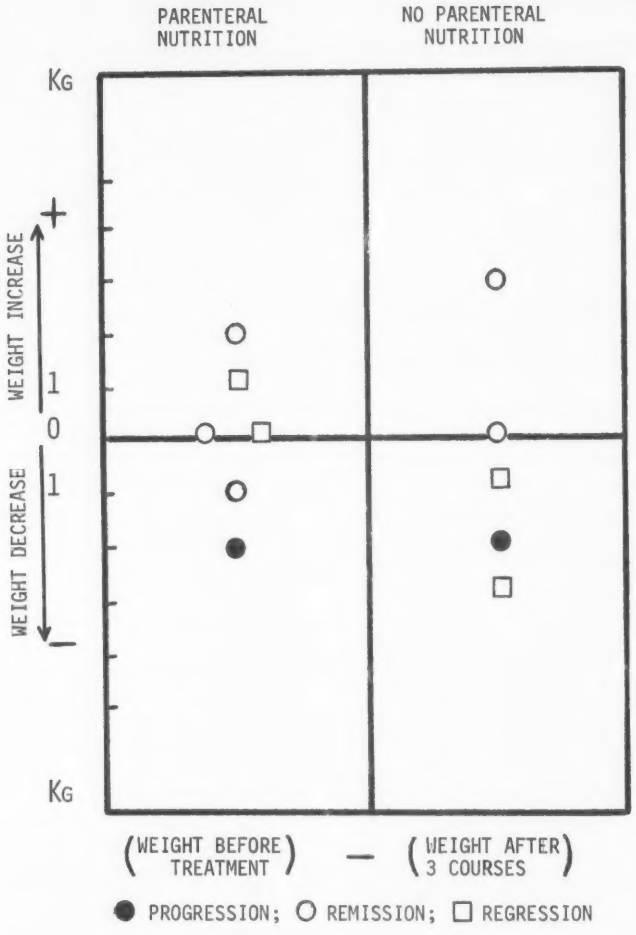

FIGURE 1.—Effects of therapy on weight

of chemotherapy on bronchogenic small-cell carcinoma. The majority of patients were in complete remission after three courses of intensive chemotherapy. This occurred without any major toxicity and without having to place the patient in a protected environment. In each group we encountered one patient who did not respond to therapy. The patient who died in the PIVN group did not seem to show any beneficial effects from this therapy.

PIVN was well tolerated, the technique is simple (venipuncture of a peripheral vein does not require catheterization), is reasonably priced, and does not oblige the patient to be admitted to the hospital. We have previously shown that this nutritional program can be easily implemented for ambulatory patients without any major complications (3-5). We have also previously shown in nonrandomized, but matched patient group study that there is an increased partial remission in patients with either epidermoid tumors of the head, neck, and lung or advanced alimentary tract tumors (5).

In the trial presently in progress we have not been able to demonstrate any protective activity by PIVN against toxicity due to chemotherapy or its suppressive effects on blood cell lines. There does not appear to be any difference between the two test groups. Al-

though preliminary, these results suggest that PIVN does not augment tumor sensitivity to the drugs employed. Our results, therefore, do not confirm the preliminary results we previously reported (3-5) and which were along the same lines as other authors (1,2). Instead we seem to be more in line with the preliminary result of Validivieso et al (7) who worked with the same tumor, using the same chemotherapy, but employed a more aggressive PIVN under the French-American Agreement.

Some reported results suggest that PIVN can stimulate tumor growth, most likely by bringing more resting cells into the cell cycle or possibly by other mechanisms leading to modulation of the immune response (6). On the other hand it is possible that parenteral nutrition should be more aggressive for chemoresistant tumors as compared to protocols employed in bronchogenic small-cell carcinoma. This could explain the results we and others have observed in more chemoresistant tumors, such as digestive and epidermoid cancers (1-5). Within this context, association of parenteral nutrition to chemotherapy beginning to get some efficacy could present a certain interest in the case of both epidermoid as well as digestive tumors. An efficacious application of this kind of treatment may ensue from studies employing strictly randomized populations in precisely defined trials. Nevertheless, it would be premature to conclude that parenteral nutrition has no place in the treatment of chemosensitive tumors. Indeed, the number of patients will have to be increased and results carried into the longterm.

A very practical outcome of our study is our demonstration that PIVN is a relatively simple technique that is well tolerated by the patient and can be applied to other areas of cancerology.

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Summary of Discussions on the Nutritional Support and Cancer Therapy Session of the Conference on the Nutrition of the Cancer Patient

William D. DeWys[1,*]

Nutritional support was discussed at several sessions, but these discussions have been combined in the following resume because of overlap and interrelationships.

In discussing the animal model work presented by Dr. Popp, Dr. Fischer suggested studying different nutritional substrates with the goal of preferential support of host tissues rather than tumor tissues. Dr. Popp responded that he has planned such studies but has no data to report. Dr. DeWys commented that a study of selective amino acid deprivation in patients with malignant gliomas supported by DNCP suggests slightly improved survival in the amino acid deprived patients and that manipulation of amino acids merits further study.

Dr. John Grant suggested that metabolic response to administration of nutrients into the systemic circulation in parenteral nutrition may differ from entry of nutrients into the portal circulation and encouraged study of intragastric administration of nutrients in animal tumor models. He asked Dr. Popp to comment on the relative distribution of retained nitrogen between muscle mass versus visceral proteins such as liver and heart. Dr. Popp noted the importance of this question but has not performed this type of analysis.

Dr. Cameron noted that in his animal model, positive nitrogen balance has been elusive, in contrast to the clearly positive nitrogen balance reported by Dr. Popp. He speculated that the difference in results might be related to difference in tumor growth rates. The model he has studied has a rapid growth rate with a high turnover of cells. Dr. Popp concurred and added that several models should be studied to provide a choice for selecting models most resembling human disease. Dr. Brennan added that most small animal TPN models previously studied have had inadequate nutritional support in the control (tumor-free iv-fed) group. Therefore, there probably was a problem of adequacy of the model.

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The reduced motor activity observed by Dr. Morrison and Dr. Popp was discussed in relation to lactate metabolism. Dr. Morrison reported that he had estimated daily lactate production by the tumor based on the perfusion studies of Dr. Gullino. He found that the heat of combustion of the estimated 24-hour lactate correlated very well with the reduction in energy expended on motor activity. He concluded that energy available for motor activity has been replaced by energy being consumed in futile cycling which then appears as increased resting energy expenditure. Increasing nutrient intake per se does not restore motor activity. Dr. Morrison is planning to study forced motor activity in an animal model to see if this can restore the partitioning of energy between the resting and activity components of energy expenditure.

Dr. Holroyde continued the discussion of elevated resting energy expenditure, noting that with hyperalimentation, resting energy expenditure is increased even more. He noted that wasted energy expenditure may deprive cells of the energy needed for ion pumping and suggested that this may be a factor in the abnormalities observed in normal cells in cancer patients. He suggests further study of metabolism of normal cells in cancer patients.

Dr. Schersten reported during the discussion period on studies he has performed using a 14-day period of TPN in cancer patients. Prior to treatment, the patients were in negative energy balance. Patients were given 40 kcal/kg body weight/day of a formulation providing 240 kcal/g of nitrogen, 25% glucose, 63% fat, and 12% amino acids. All patients increased their energy expenditure, most increased their resting metabolic rate, and all but one had improved energy balance. Body weight increased, but body cell mass was unchanged, suggesting retained water and/or fat as the increased body weight. However, he found increased protein synthesis by muscle. Although he has not measured protein breakdown in muscle in this study, he speculated that this was also increased to explain the lack of change in body cell mass. He also has noted decreased magnesium and phosphorous in normal tissues at autopsy in cancer patients, which agrees

with the observations of Nixon and Lawson presented at this conference. He speculated that aberration of ATP metabolism in normal tissues such as myocardium could be a cause of death in cancer patients.

Dr. Kisner continued the discussion by asking why lean body mass was not consistently synthesized by nutritionally supplemented cancer patients (some do, as pointed out in Dr. Brennan's paper, but some do not). He noted that Lundholm et al have shown that depressed protein synthesis in normal tissues of cancer patients could be improved by adding excess amino acids or by adding insulin in vitro. Dr. Lundholm responded that there is a block of protein synthesis in the liver. The rate of initiation of protein synthesis in hepatocytes from cancer patients is reduced. Lundholm and his colleagues are currently trying to identify this block in protein synthesis which affects muscle, liver, lymphoid tissue, and the gastrointestinal tract.

Dr. Murray Selzer raised questions as to experimental design in TPN trials. He questioned the adequacy of the caloric intake and the timing of TPN relative to chemotherapy. In response, Dr. Valdivieso reviewed a series of studies which suggest that giving IVH prior to chemotherapy may reduce the myelotoxicity from chemotherapy, but reduced myelotoxicity is not seen if TPN and chemotherapy begin concurrently.

Dr. Kisner continued the discussion of timing of TPN by suggesting that tumor cell kinetics should be studied during TPN. He noted that TPN could stimulate tumor growth and the timing of chemotherapy could then be based on changes in the kinetics of the tumor cells.

Continuing the discussion of experimental design, Dr. DeWys pointed out the need for adequate numbers of patients in TPN studies. He postulated that nutritional support of malnourished patients might improve their response to therapy to be comparable to that of patients who were not malnourished. The magnitude of this improvement might be a 20% improvement in response rate or several months improvement in median survival. For this difference to reach statistical significance requires a larger number of patients than have been studied in most series reported to date and may required multi-institutional collaboration.

The infections observed by Dr. Valdivieso in the TPN group were discussed further. These were predominantly *Pseudomonas* organisms causing pneumonia and the frequency of *Pseudomonas* was very high compared to the usual frequency of this organism at the M.D. Anderson Hospital. Dr. DeWys questioned whether these infections were related to an elevated blood glucose level in the TPN patients. Dr. Valdivieso has not analyzed his data for this variable. A physician asked whether the infections might be related to hypophosphatemia. Hypophosphatemia is a known metabolic effect of TPN and causes neutrophil dysfunction. Dr. Valdivieso observed hypophosphatemia in a few of his patients, but did not observe any correlation with infection.

Returning to the question of adequacy of caloric supply via TPN, Dr. Waterhouse commented that providing a daily energy excess of 1000 kcal/day over a few weeks may not be sufficient for rebuilding lean body mass. Nutrition should be viewed as chronic therapy, not acute therapy. She also suggested measuring plasma amino acids, insulin, and glucose in patients receiving TPN. Dr. H. Douglas continued this line of discussion, proposing trial of long-term (4 to 6 months) enteral nutrition on outpatients.

In conclusion, replenishing the metabolic deficiencies of the cancer patient is clearly not a simple process. Failure of replenishment may be related to altered host metabolism which is only partially understood. Failure may also occur because the nutrients delivered do not have the optimal composition, the route and schedule of delivery are not optimal, the duration of therapy is not sufficient, and/or the timing relative to treatment aimed at ablating the cancer is not optimal. Research aimed at these issues is in progress and further research is encouraged.

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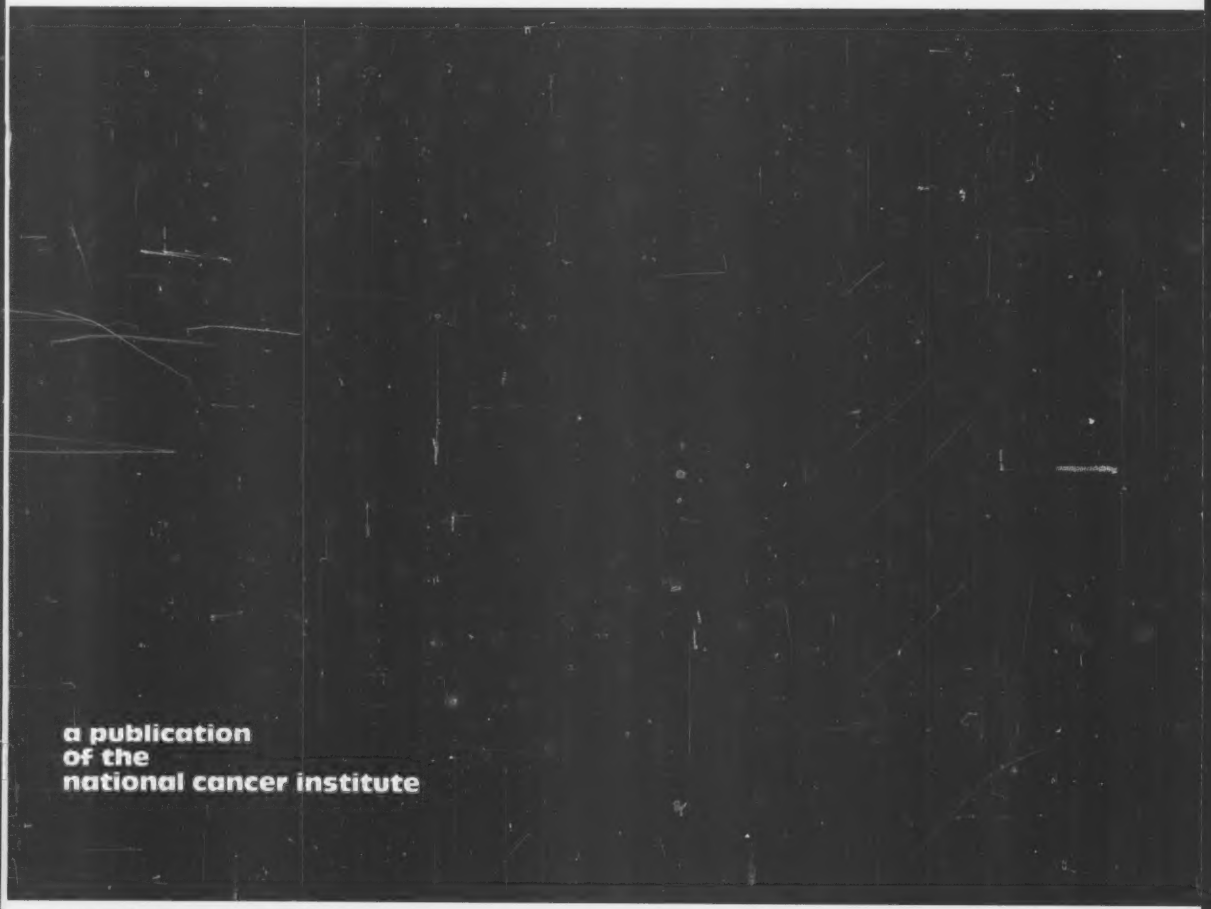

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